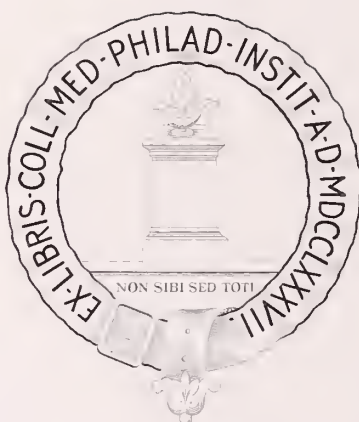


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Hypothyroidism in Infancy

ANDREW S. BREM, M.D.* and JAMES E. HADDOW, M.D.**

INTRODUCTION

The diagnosis of congenital thyroid insufficiency is often difficult to make in the first weeks following birth. Obvious signs and symptoms such as constipation, bradycardia, and temperature instability may also apply to other clinical entities. Myxedematous changes occur usually only after several weeks of life and by then the diagnosis is evident. Yet prognostically, it is imperative for the correct diagnosis to be made as early as possible. A statistically significant difference in the mean intelligence quotient has been demonstrated between infants diagnosed and treated before age three months and those after three months of age.^{1,2} The purpose of this paper is to arouse suspicion for the subtle clinical changes and discuss mechanisms for congenital hypothyroidism.

CLINICAL PRESENTATIONS

Congenital hypothyroidism has an incidence of approximately 1:8500 births.³ In the neonatal nursery, tachypnea, cyanosis, bradycardia and a hoarse cry are suggestive signs. Constipation, temperature instability, and prolonged physiologic jaundice are important diagnostic observations in the first weeks of life. While the vast majority of hypothyroid neonates do not present with a neck mass, congenital goiter is a finding of significant import in the nursery. During the first months of life, less specific observations can be made, often by a parent. Progressive lethargy, poor feeding and weight gain together with retarded linear growth are such early observations of thyroid insufficiency. An umbilical hernia may also become noticeable. Table 1 lists many of these historical and physical findings.

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TABLE 1

CLINICAL PRESENTATION OF HYPOTHYROIDISM IN THE FIRST SIX MONTHS		
A.	% in	% in
	Normals	Hypothyroidism
Symptoms:		
Lethargy	0	96
Feeding Problems or Poor Weight Gain	5	83
Hoarse Cry	0	67
Constipation	2	42
Prolonged Jaundice	0	12
B.		
Signs:	% in Hypothyroidism	
Umbilical Hernia		70
Retarded Linear Growth		60
Hypothermia		55
Bradycardia		50
Respiratory Embarrassment		50
Goiter		5

Forty-nine cretins were studied by Lowrey and his workers in the 1950's.⁴ They concluded that 95% of hypothyroid infants displayed three or more signs or symptoms of hypothyroidism before the end of the third month. In the first month, 54% developed signs and symptoms leading to the diagnosis.

ETIOLOGIES

Causes of congenital hypothyroidism are many but may generally be divided into the three categories listed in Table 2. The most common abnormality lies in the embryonic development. About 60% to 80% of congenital hypothyroidism results from thyroid agenesis or dysgenesis.^{5,6} In such cases, residual thyroid tissue may be demonstrated either ectopically or in the usual position by radioactive scan. Drugs such as propylthiouracil and iodine can cross the placenta and interfere with fetal thyroid hormone production.⁵ A number of rare autosomal recessive biochemical

TABLE 2

CAUSES OF CONGENITAL HYPOTHYROIDISM		
<i>Thyroid Gland</i>		<i>Hereditary Biochemical Defects In</i>
<i>Development:</i>	<i>Drugs:</i>	<i>Thyroid Hormone:</i>
Agenesis	Iodine	Trapping
Dysgenesis	Radioactive Iodine	Organification
	Antithyroid Drugs	Coupling
		End Organ Resistance
		Thyroglobulin Defect
		Deiodination

lesions make up the third category. Defects in the trapping of the iodide ion, organification of the iodide ion onto tyrosine molecules, coupling of the tyrosine monomers and abnormalities in the colloid thyroglobulin all preclude the synthesis of hormone. End organ insensitivity to thyroid hormones or TSH and inability to deiodinate compounds for recycling of iodine also may produce hypothyroidism.^{5,7}

NORMAL DEVELOPMENT AND PHYSIOLOGY

Approximately three weeks after conception, the primitive thyroid can be seen migrating from the floor of the pharynx in the area of the first and second pharyngeal pouches.⁵ After the seventh week of gestation, the fetal thyroid forms cords of dividing parenchymal cells, and colloid production begins.^{5,8} Thyroid stimulating hormone (TSH) and thyroid binding globulin (TBG) can be measured in the fetal blood at three months.⁸ Parallel fluctuation between free (unbound) thyroxine, the biologically active hormone, and TSH have been documented after twelve weeks gestation.⁹ As little if any thyroxine or maternal TSH cross the placenta, the presence of a functioning fetal thyroid pituitary axis is confirmed.^{9,10} High levels of free circulating thyroxine act on the hypothalamus blocking the release of thyrotropin releasing factor (TRF). An absence of TRF prevents the pituitary release of TSH, and the thyroid gland is not stimulated. With low free circulating thyroxine, hypothalamic receptors trigger the feedback mechanism to produce more TSH from the pituitary and thereby stimulate thyroid hormone production.

Throughout development, fetal protein binding of thyroid hormone changes. Between eleven and twenty-four weeks, thyroid binding prealbumin and albumin bind thyroxine.⁹ TBG serum concentration increases rapidly, however, between twelve and twenty-four weeks and is more highly specific for thyroid hormone binding.^{9,10} After twenty-four weeks gestation, thyroxine binding capacity increases without a change in TBG serum levels. Thus, there is a shift in the type and affinity of thyroid binding proteins as the fetus matures.

TSH, thyroxine and triiodothyronine cross the placenta only in minute amounts.^{7,9,10,11} This is due in part to differences between maternal and fetal binding proteins and the physical impermeability of

TABLE 3

COMPARISONS BETWEEN FETAL AND MATERNAL SERUM LEVELS OF THYROID RELATED HORMONES. (mean \pm ISD)			
<i>MATERNAL</i>			
Weeks	11-18	22-34	38-40
Total Thyroxine micrograms/100 ml	12.9 \pm 1.1	12.2 \pm 0.51	11.5 \pm 0.56
Free Thyroxine millimicrograms/100 ml	2.97 \pm 0.27	2.82 \pm 0.12	2.30 \pm 0.13
TSH micrograms/100ml	4.2 \pm 0.68	3.8 \pm 0.38	4.3 \pm 0.40
<i>FETAL</i>			
Weeks	11-18	22-34	38-40
Total Thyroxine micrograms/100 ml	2.6 \pm 0.24	7.2 \pm 0.61	11.2 \pm 0.43
Free Thyroxine millimicrograms/100 ml	1.85 \pm 0.17	2.49 \pm 0.17	2.90 \pm 0.10
TSH microunits/ml	2.4 \pm 0.14	9.6 \pm 0.93	8.9 \pm 0.93

the placenta to thyroid hormones.^{7,9,12} Table 3 demonstrates comparisons between maternal and fetal levels of TSH, free thyroxine and thyroxine at various stages of pregnancy.

MECHANISMS OF THYROID HORMONE ACTION

The thyroid gland exerts its effect on every major organ system. Both triiodothyronine and L-thyroxine attach to specific nuclear binding sites.¹³ Once bound, these hormones augment the transcription of genetic information. Nuclear RNA is synthesized and the entire process of protein production is stimulated.

In the fetus and infant, there is rapid growth in the central nervous system. Neural cell proliferation and DNA synthesis continues to about five months after birth.⁸ The production of central nervous system interstitial supportive tissue also occurs in this time period. Thyroid hormone has far reaching effects on this phase of central nervous system growth. Autopsies of cretins demonstrate defective myelination, reduced capillaries, and poorly developed axons and dendrites.⁸ Decreased protein synthesis and defective neural development in this thyroxine dependent growth phase offer the best explanation for the central nervous system signs and symptoms in hypothyroid infants.

Respiratory distress and cyanosis may be early signs of congenital hypothyroidism. Thyroxine influences the synthesis of surfactant, a surface active phospholipid, in the type II pneumocyte.^{14,15} Absence of surfactant raises surface tension along the air-fluid interface in the air sacs, producing alveolar collapse on expiration. Further respiratory embarrassment may result from myxedematous infiltrates beneath the nasopharyngeal mucosa and vocal cords.⁵ As neonates are almost exclusively nose breathers, these infiltrates induce a form of nasal obstruction leading to respiratory distress. Another potential cause of alveolar hypoventilation in hypothyroidism is the depression of hypoxic ventilatory drive, a central nervous system effect.^{16,17} Any of

the above mechanisms could contribute to the infant's distress in the nursery.

Myxedematous intestinal wall infiltrates also alter neuromuscular function resulting in constipation.^{5,18} A more subtle sign of gastrointestinal hypomotility in the hypothyroid neonate is prolonged unconjugated hyperbilirubinemia.¹⁹ A lack of hepatic enzymes secondary to decreased protein synthesis may prevent adequate conjugation of bilirubin. In addition, the neonate intestinal mucosa normally contains an enzyme, Beta-glucuronidase which hydrolyzes conjugated bilirubin.¹⁹ With hypomotility, a greater fraction of the conjugated bilirubin may be acted upon by the Beta-glucuronidase, converted to the unconjugated form, and reabsorbed into the circulation from the intestine. Both mechanisms can contribute to the hyperbilirubinemia of neonatal hypothyroidism.

Generation and maintenance of body heat is a function of thyroid activity.²⁰ Within minutes following delivery, increased amounts of TSH are normally released into the infant's circulation, followed by a rise in circulating thyroid hormone over the ensuing 24 hours. Part of this physiological phenomenon may be an adaptation for heat production. It has been postulated that heat is generated through energy expended in pumping sodium ions out of cells.²¹ Thyroid hormones acting upon intracellular nuclear receptor sites stimulate synthesis of proteins^{12,20} which may insert in key areas of the cell membrane or activate the sodium ion pumps. High energy phosphate bonds are hydrolyzed to fuel the process, and heat is released as part of this reaction.

Hypothyroidism produces a lowered metabolic demand for oxygen, which results in a proportional drop in cardiac output.⁵ Murmurs are frequently heard which with the previously described cyanosis and respiratory distress may prompt referral for congenital heart disease.²² Electrical conduction changes can be present on the electrocardiogram. In addition to the bradycardia and low voltage frequently seen, a dome shaped ST segment called the mosque sign may be noted.²³ Both murmurs and electrical changes are thought to be due to myxedematous infiltrates.

DIAGNOSTIC TESTS

Several diagnostic screening tests can be applied to confirm the clinical diagnosis of congenital hypothyroidism in infancy. Normal serum thyroxine and TSH values have been established for both newborns and prematures.^{11,12,21} These normal values differ considerably from older children and adults. Table 3 gives normal numerical ranges adjusted for gestational age. Thyroxine and TSH can now be measured accurately with microtechniques allowing for population screening.^{3,24} The normal mean serum T4 derived from this population survey for infants ages 3-6 days was 11 micrograms/100ml, thus supporting earlier observations that circulating

thyroid hormone levels are elevated in the early weeks of life. Both mean figures and the normal range of values are increased early in life, giving rise to much confusion in interpretation by those unfamiliar with the newborn. A T4 value lower than 9.8 micrograms/100ml in the first two weeks and less than 8.2 micrograms/100ml in the second two weeks of life should make one suspect hypothyroidism. X-ray of the distal femoral and proximal tibial epiphyseal plates for calcification is helpful. Bone calcification in these centers may be absent in hypothyroid neonates due to retarded bone growth in utero. Radioactive scanning for the presence and locale of thyroid tissue in the face of low thyroid hormone values aids in the diagnosis of thyroid agenesis or dysgenesis.

TREATMENT

Thyroid replacement should begin as soon as the diagnosis is made. Therapy consists of either dessicated thyroid 10 mg/kg per day or L-thyroxine 15 micrograms/kg per day. Thyroxine and TSH levels should be obtained within two weeks for dosage adjustments. Intrauterine treatment utilizing thyroxine injected into amniotic fluid is an experimental therapy for future consideration.²⁵

CONCLUSION

The early diagnosis of congenital hypothyroidism is difficult but critical. With an incidence of 1:8500 live births, it is a disease sufficiently common to be considered in infants manifesting abnormalities of activity or growth. Etiologies are multiple but the vast majority are embryological errors presenting as thyroid dysgenesis or agenesis. The thyroid gland exerts an effect on all major organ systems with measurable activity beginning before the third month of gestation. Laboratory tests for hormonal function include direct assay of hormones and thyroid scans. Treatment for congenital hypothyroidism must be initiated before age three months to assure normal or near normal central nervous system development.

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Warnings: Estrogen therapy should not be given to women with recurrent chronic mastitis or abnormal mammograms except, if in the opinion of the physician, it is warranted despite the possibility of aggravation of the mastitis or stimulation of undiagnosed estrogen-dependent neoplasia.

The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, retinal thrombosis, cerebral embolism and pulmonary embolism).

If these occur or are suspected, estrogen therapy should be discontinued immediately.

Estrogens may be excreted in the mother's milk and an estrogenic effect upon the infant has been described. The long range effect on the nursing infant cannot be determined at this time.

Hypercalcemia may occur in as many as 15 percent of breast cancer patients with metastases, and this usually indicates progression of bone metastases. This occurrence depends neither on dose nor on immobilization. In the presence of progression of the cancer or hypercalcemia, estrogen administration should be stopped.

A statistically significant association has been reported between maternal ingestion of diethylstilbestrol during pregnancy and the occurrence of vaginal carcinoma in the offspring. This occurred with the use of diethylstilbestrol for the treatment of threatened abortion or high risk pregnancies. Whether or not such an association is applicable to all estrogens is not known at this time. In view of this finding, however, the use of any estrogen in pregnancy is not recommended.

Failure to control abnormal uterine bleeding or unexpected recurrence is an indication for curettage.

Precautions: As with all short acting estrogens, the following precautions should be observed:

A complete pretreatment physical examination should be performed with special reference to pelvic and breast examinations.

To avoid prolonged stimulation of the endometrium and breasts in climacteric or hypogonadal women, estrogens should be administered cyclically (3 week regimen with 1 week rest period—withdrawal bleeding may occur during rest period).

Because of individual variation in endogenous estrogen production, relative overdosage may occur which could cause undesirable effects such as abnormal or excessive uterine bleeding, mastodynia and edema.

Because of salt and water retention associated with estrogenic anabolic activity, estrogens

should be used with caution in patients with epilepsy, migraine, asthma, cardiac, or renal disease.

If unexplained or excessive vaginal bleeding should occur, reexamination should be made for organic pathology.

Pre-existing uterine fibromyomata may increase in size while using estrogens; therefore, patients should be examined at regular intervals while receiving estrogenic therapy.

The pathologist should be advised of estrogen therapy when relevant specimens are submitted.

Because of their effects on epiphyseal closure, estrogens should be used judiciously in young patients in whom bone growth is incomplete.

Prolonged high dosages of estrogens will inhibit anterior pituitary functions. This should be borne in mind when treating patients in whom fertility is desired.

The age of the patient constitutes no absolute limiting factor, although treatment with estrogens may mask the onset of the climacteric.

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Pregnancy-Related Alpha-Fetoprotein Testing

Guidelines in Usage and Interpretation

JAMES E. HADDOW, M.D.*

In the near future it will be possible to obtain accurate measurements of alpha-fetoprotein (AFP) in maternal serum and amniotic fluid during pregnancy. The major purpose of such testing will be to detect fetal anencephaly and spina bifida at a time in gestation early enough to allow elective termination. Properly carried out, this new service can provide relief from emotional and financial stress to a significant number of families, but a number of ethical and scientific criteria must be satisfied for that goal to be realized. Before considering those criteria, a brief review of the events leading to the use of this new pregnancy test would appear worthwhile.

Three years ago Brock, in Scotland, reported that AFP levels were often elevated in amniotic fluid when the fetus was afflicted with anencephaly or spina bifida.¹ This was a particularly important observation in the United Kingdom, where the incidence of neural tube defects is 0.8 percent. Subsequent reports from other centers confirmed the accuracy of Brock's work, and such testing has now become accepted practice in selected, high risk pregnancies.^{2,5} If a woman has delivered one infant with a neural tube defect (NTD), her subsequent risk of such a problem is 5 percent; if the same woman has a second pregnancy complicated by NTD, her subsequent risk is 10 percent.¹ Occasionally, an individual with spina bifida is able to reproduce. In that case the risk of fetal neural tube malformations approaches 3 percent regardless of the sex of the affected parent.⁶ All of these situations represent high risk pregnancies, and amniotic fluid AFP determinations are now recommended as part of standard management.

A second possible application for AFP testing in pregnancy was identified in 1974 with separate reports from Brock and Seller that maternal serum AFP levels often reflected those in amniotic fluid, thus raising the possibility that unselected populations of pregnant women could be safely screened for fetal NTD.⁷⁻⁹ As a result of these observations, a combined hospital study has been undertaken in the United Kingdom to establish the value of serum screening,¹⁰ and Brock has recently indicated that, in an unselected pregnancy population, anenceph-

aly can be diagnosed with 86 percent accuracy and spina bifida with 36 percent accuracy for an overall success rate of 62 percent when abnormally high maternal serum AFP levels are used as the determinant.¹¹

Routine serum testing of AFP levels is performed currently in some locations without the knowledge or consent of individual patients. Borderline or frankly elevated serum AFP levels lead to repeated measurements which, if confirmed, require that further decisions involving testing and intervention involve the family at risk.¹² Our opinion is that no testing should be undertaken, either as a screening measure or in high risk individuals, without the patient's informed consent. The fetal neural tube defect is fixed and cannot be altered by therapy; and any decision relating to pregnancy intervention should rest with the parents. If a family is not prepared to follow through, then no testing should be undertaken.

It is important that the time of gestation be known with reasonable accuracy, if serum and amniotic fluid AFP levels are to be interpreted correctly.¹³ Prior to 13 weeks gestation both amniotic fluid and serum levels are relatively low, and pregnancies complicated by neural tube lesions cannot be detected. After 13 weeks gestation, AFP concentrations become diagnostically valid, but even then the time of pregnancy must be known with reasonable certainty, since normal ranges vary with gestational age. Ideally, sampling of either serum or amniotic fluid should occur between 14 and 16 weeks gestation to allow sufficient time for further confirmatory testing leading to possible decisions concerning abortion. The necessity of establishing the time of pregnancy places an added burden upon the physician, who must rely on a combination of historical and physical findings to arrive at a figure whose accuracy has traditionally been less than perfect.

Two serum samples, taken a few weeks apart, should be obtained routinely when any pregnancy is being screened for neural tube defects. By so doing the worst mistake, that of overestimating gestational age, could be overcome; and the second sample would be expected to compensate for such a miscalculation. The test could not be expected to overcome all errors in gestational timing, even if repeated at three week intervals since normal values rise steadily between 14 and 20 weeks; but the second sample might still increase the chances of

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diagnosing fetal NTD sufficiently to make its use worthwhile.

In cases where a pregnancy at high risk for fetal neural tube malformations has been identified or where abnormal serum screening has led to further investigation, amniocentesis becomes the diagnostic procedure of choice. Whenever feasible, ultrasonography should be performed in conjunction with amniocentesis for several reasons.^{14,15} This procedure localizes the placenta enabling safe placement of the sampling needle. Avoidance of the products of conception is critical when amniotic fluid is to be assayed for AFP levels, since contamination with fetal blood can lead to falsely elevated values (not to mention significant direct damage to the conceptus). It also helps to establish gestational age more accurately. It identifies multiple pregnancies and can help determine whether the fetus is viable. Finally, in some cases it can, by itself, diagnose a neural tube malformation. Any bloody amniotic fluid sample must be viewed with extreme suspicion, and Brock has suggested that all amniotic fluid specimens be tested for the presence of fetal hemoglobin to avoid misinterpretation of results.¹⁶ The identification of twin pregnancies can be helpful not only because such situations have on occasion been associated with high-normal maternal serum AFP values but also because a case has occurred where fluid in one amnion had a normal AFP level while in the second amnion, levels were elevated.¹⁴ In that situation, each sac could be entered separately and AFP levels measured for each conceptus individually. Distressed or dead fetuses give rise to elevated AFP levels (and, incidentally, elevated amniotic fluid total protein levels),⁵ and ultrasound can frequently help to identify such problems. Sonography may also help to avoid needle placement in a full bladder during amniocentesis. Maternal urine grossly resembles amniotic fluid, and AFP levels in such a sample would be very low, giving rise to much confusion.¹⁶ Unusually low maternal serum AFP levels occur with hydatidiform moles and choriocarcinoma,¹⁷ and ultrasound can also be helpful in diagnosing those problems.

Normal levels of serum or amniotic fluid AFP cannot rule out the possibility of NTD. Percentage accuracy in diagnosing these lesions using maternal serum has been mentioned already. In high risk pregnancies where amniotic fluid is sampled as a first step, the ability to diagnose NTD is better, but still a significant number of those anomalies will remain unidentified. Apparently, a certain critical area of neural membrane must be exposed to allow transudation of fetal proteins into the amniotic fluid. The limitations as well as the virtues of AFP testing must be appreciated by all concerned, lest expectations be unrealistically high; as matters now stand, a certain number of infants will still be born with NTD even if all aspects of population screening and high-risk testing are carried out optimally. To

date only a few examples have been reported where falsely high amniotic fluid AFP values led to the abortion of a normal fetus, and in some of those cases screening for fetal hemoglobin might have avoided the problem.¹⁶ The fact remains, however, that under the best of conditions such an outcome might uncommonly occur, and everyone must be prepared for that eventuality. It would be desirable ideally to have further diagnostic confirmation of fetal NTD before recommending abortion. In the future radiographic contrast techniques,¹⁸ fetoscopy and further refinements in ultrasonography may offer that confirmation. Presently, however, amniotic fluid AFP elevations represent the single most reliable indicator of such malformations.

Besides neural tube defects several other fetal malformations have been associated with elevated AFP values. Congenital nephrosis, an uncommon but lethal disorder inherited as an autosomal recessive, produces high concentrations of amniotic fluid AFP through leakage of circulating fetal proteins into fetal urine.¹⁹ Omphalocele has been similarly associated with high levels resulting from protein leakage across exposed membrane surfaces,²⁰ and both esophageal²¹ and duodenal atresias²² have produced elevated AFP levels by an obscure mechanism. With the exception of congenital nephrosis, those other lesions have so far been documented as having high AFP values only later in pregnancy.

Hepatitis can give rise to elevated circulating AFP values in any individual, particularly during the healing phase.²³ The pregnant woman is no exception, and in the unusual case where pregnancy and hepatitis occur simultaneously, maternal serum AFP values may be clearly elevated in the absence of fetal anomaly. The amniotic fluid AFP level would be expected to be normal under such circumstances, hopefully preventing further confusion. Malignant tumors are uncommon in pregnant women but certain such neoplasms, (i.e., hepatoma, germ cell tumors) are capable of producing circulating AFP in large amounts. It is not known whether under those circumstances amniotic fluid AFP values would also be increased. A fetomaternal transfusion might also create abnormal maternal serum values.

Inevitably a certain percentage of maternal serum AFP levels in any screening program will be repeatedly at or above two standard deviations from mean values in the absence of disease. Brock has estimated that this will give rise to 20 aminocenteses/1,000 pregnancies screened. In Edinburgh this results in a ratio of 4.5 normal/one abnormal amniotic fluid AFP sample (assuming 62 percent detection efficiency).¹¹ The ratio will be higher in the United States where the incidence of NTD is somewhat lower, but the overall merits of disease detection should still outweigh procedural complications.

The many facets of alpha-fetoprotein interpretation in pregnancy require that any physician who

orders such a test have more than a passing acquaintance with its complexities. The preceding discussion has already stressed the necessity of obtaining patient permission before doing the test and of identifying gestational age as accurately as possible. Any laboratory which processes such samples must have established normal ranges of AFP throughout pregnancy both for serum and amniotic fluid and must exercise strict quality control over all testing. Prompt reporting of abnormal values must be provided, and it may often be necessary for the laboratory and the family doctor to discuss results if patients are to receive full benefit from this new service.

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Hemoglobin-Oxygen Affinity and Tissue Oxygen Delivery*

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ABSTRACT

The relative influences of shifts in hemoglobin-oxygen affinity on tissue oxygenation in the living animal have yet to be established. Because of its sigmoidal shape, a rightward shift of the oxyhemoglobin dissociation curve will cause more oxygen to be released per mmHg drop in oxygen tension from fully saturated blood, but less oxygen, relative to a normal or left-shifted curve, from poorly saturated blood. To evaluate the physiologic role of hemoglobin-oxygen affinity in hypoxia, two series of experiments were conducted in which affinity was changed chronically or acutely in rabbits exposed to either progressive or maintained hypoxia. Tissue oxygen availability was measured with chronically implanted brain, muscle, and kidney polarographic electrodes. These studies demonstrated (1) that the animals were able to compensate for restricted oxygen release by increasing cardiac output, (2) that slightly higher levels of tissue oxygen availability were maintained by animals with high hemoglobin-oxygen affinity at moderately hypoxic levels, but (3) that at severely hypoxic levels, no advantage from shifts in affinity in either direction were apparent. Recovery during subsequent normoxia was more complete, however, in low affinity animals. Current studies in this area, involving isolated heart preparations, will be described.

Today it is common knowledge that oxygen is carried from the lungs to the tissues by hemoglobin within the red cells. Although the varying colors of circulating blood have been recognized for countless centuries, the association of these red and purple pigments with tissue respiration was not confirmed until just over a century ago, when hemoglobin was crystallized and its ability to combine reversibly with oxygen demonstrated.¹ The important added discoveries that the strength of this hemoglobin-oxygen bond varied with pH and with carbon dioxide concentration were not made until the first decades of this century,^{2,3} and it has been only within the last seven years that influence of intraerythrocytic organic phosphates on oxygen affinity has been recognized.^{4,5} Intensive research today is focused on the biochemical functions of hemoglobin as they are affected by its molecular structure and the several ligands which bind its four component protein chains.

It is frustrating to realize that despite this vast amount of research and the functional hypotheses which may be drawn from it, that the true influence of hemoglobin-oxygen affinity on tissue oxygenation has yet to be identified. If, indeed, it can be shown that oxygen delivery may be improved through biochemical modifications of the hemoglobin molecule, then an important step will have been completed toward the development of a new therapeutic approach for the relief of tissue hypoxia. The purpose of this report is to present information we have gained from experiments in this area during the last three years and to describe a change in the direction of our research which has resulted from these findings.

Two series of experiments have been carried out, each using rabbits with chronically implanted tissue oxygen electrodes. The first study was designed to find out if animals with previously induced high or low hemoglobin-oxygen affinity respond differently to a gradual decrease in inspired oxygen concentration, and the second was planned to look more carefully at the effects of an abrupt shift in hemoglobin-oxygen affinity brought about during maintained hypoxia.

The reasoning behind these experiments is best understood by reviewing the oxyhemoglobin dissociation curve and the changing relationships between oxygen saturation and oxygen tension as the position of the curve is shifted to the right (a decrease in affinity) or to the left (an increase in affinity). First, a rightward shift will result in more oxygen being available for release per unit drop in oxygen tension, but *only* if one starts with fully saturated blood. It is less commonly recognized that this situation is reversed if oxygen is to be delivered from poorly saturated blood, that is, along the lower bend of the oxyhemoglobin dissociation curve. By the same token, a leftward shift in the curve, that is, increased hemoglobin-oxygen affinity, may be expected to result in more efficient oxygen delivery from poorly oxygenated blood and may be of added benefit in hypoxia since oxygen uptake in the pulmonary capillary will be greatly enhanced. It is this latter possibility which our experiments have been designed to explore.

All rabbits had fine platinum polarographic electrodes implanted in brain, kidney, and muscle tissues at least two weeks prior to each experiment.⁶ The same basic preparation, seen in Figure 1, served both studies. pH and blood gas analyses were performed with Instrumentation Laboratories equipment (Model 125 polarograph, 123 electro-

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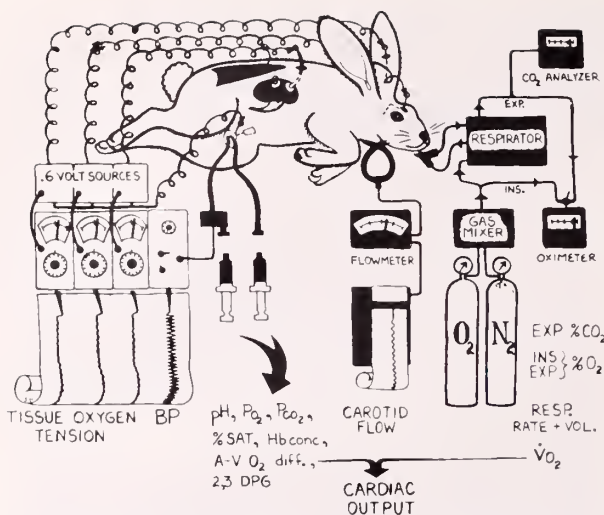


Fig. 1. Experimental preparation for in vivo hemoglobin-oxygen affinity studies.

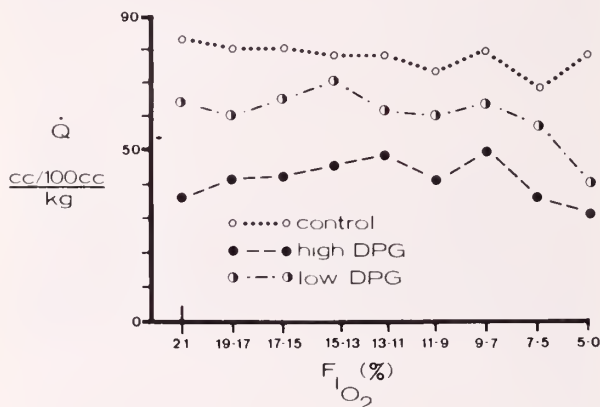


Fig. 2. Cardiac output response to graded hypoxia. Note higher levels maintained by high affinity (low DPG) animals.

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meter, 182 CO-oximeter), respired oxygen content was measured with a Beckman Model D2 paramagnetic oxygen analyzer, and currents from the tissue oxygen electrodes were amplified and recorded using Sanborn Co. Inc. instruments.

In the first study,⁷ hemoglobin-oxygen affinity was either increased (6 rabbits), decreased (7 rabbits), or not modified (4 rabbits) during the 24 hours immediately preceding the experiments by subjecting the animals to high levels (120-150 mmHg) of carbon dioxide in oxygen, (2,3-DPG depletion), to low levels (70-80 mmHg) of oxygen in nitrogen (2,3-DPG stimulation), or to room air, respectively. These procedures resulted in the following in vivo P_{50} levels, as projected from arterial oxygen tension and saturation values obtained during the subsequent graded hypoxia: for the high affinity group, 24 (19-28) mmHg, for the low affinity group 37 (33-39), and for the normal affinity group 33 (32-34) mmHg.

Following anesthesia and surgical preparation, each animal was ventilated with 21 percent oxygen

in nitrogen for one-half hour, during which time three sets of control measurements were made. Subsequently, the concentration of oxygen in the inspired gas was reduced by 2 percent every 10 minutes until pure nitrogen was being delivered. Measurements were made prior to each change. The data obtained from this study suggested that those rabbits with blood cells which more avidly bound oxygen responded to hypoxia with increased levels of cardiac output (Figure 2) and, at moderate levels of oxygen deprivation (14-8 percent inspired oxygen), may actually have enjoyed higher levels of oxygen in their tissues (Figure 3). Considerable overlapping in the polarographic records makes the evidence of this last point tenuous, however, and it is not supported by the subsequent course of the animals which revealed no particular advantage for either group as inspired oxygen was critically reduced.

Since the slightest suggestion that tissue oxygen delivery under hypoxic conditions may be improved by leftward shifts of the oxyhemoglobin dissociation curve would demand further study, we modified our protocol for a second series of studies⁸ by providing for an abrupt change in hemoglobin-oxygen affinity, to be imposed during a constant level of hypoxia equal to that at which the previously observed differences in tissue oxygen levels had occurred.

In this series (Figure 4), affinity was not altered pre-experimentally but all animals were again started off with one-half hour of normoxia for the gathering of control data. Following this, inspired oxygen was abruptly diminished to 12 percent, and, after 15 minutes of stabilization, further measurements were made for 30 more minutes. At this point, each animal received a rapid, 100 ml exchange transfusion with donor blood pretreated to have high oxygen affinity (5 rabbits), low oxygen affinity (5 rabbits), and normal oxygen affinity (6 rabbits). The post-transfusion P_{50} levels achieved by this technique averaged 22, 36, and 33 mmHg, respectively. Samples were drawn and measurements made immediately after exchange and three times during the next half hour while hypoxia was maintained. Thereafter, to evaluate relative hemodynamic recovery, inspired oxygen was returned to 21 percent for a brief period before the experiment was terminated.

During the hypoxic post-exchange period of this study, the hemodynamic and tissue oxygen responses which had been observed in the previous graded-hypoxia experiments did not occur (Figure 5). Rather, regardless of the degree of oxygen affinity of the transfused blood, all animals responded with a drop in cardiac output and no discernible differences in tissue oxygen availability.

These results do not support the concept, therefore, that a leftward shift of the oxyhemoglobin dissociation curve may benefit tissue oxygenation in the face of severe hypoxia, either through enhanced

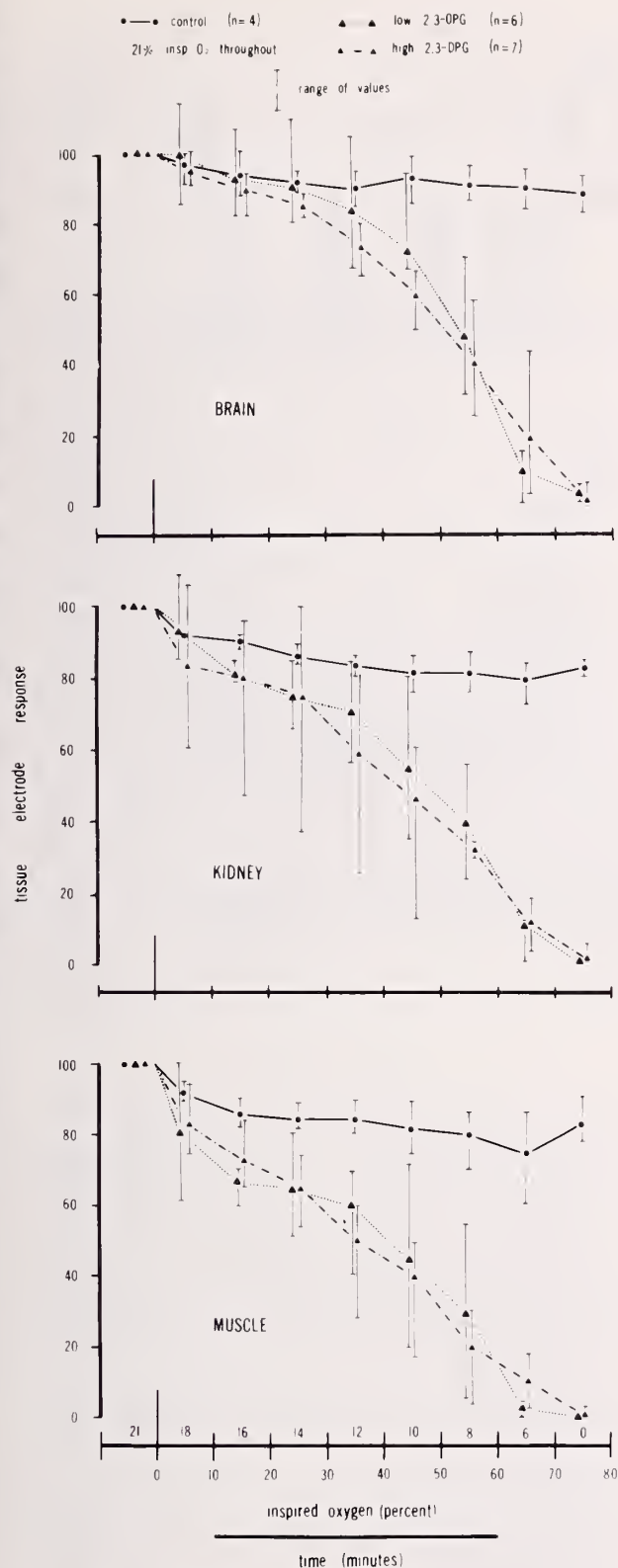


Fig. 3. Tissue oxygen electrode responses to graded hypoxia. Note higher levels maintained by high affinity animals between 14 and 8 percent inspired oxygen.

pulmonary oxygen loading or enhanced capillary oxygen release. Apparent discrepancies between our two studies may be explained by the deeper

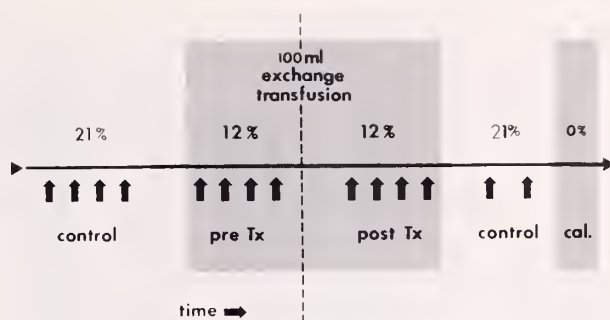


Fig. 4. Plan for second Hypoxia Study.

levels of hypoxia reached in the exchange transfusion experiments, as evidenced by venous oxygen tension which reached 14 mmHg in the high affinity recipients. At such low tensions, tissue oxygenation may have been limited by the loss of an effective partial pressure gradient, or, if the supply of oxygen first became critically limited in the myocardium, by inadequate peripheral perfusion.

In this second study, although no real differences between the groups were noted while inspired oxygen concentrations were limited, an impressive recovery of tissue oxygen readings occurred in the low affinity group during the second normoxic period. The physiologic significance of this finding is that it occurred simultaneously with a return to normal levels of oxygen consumption, with no increase in cardiac output, and with a marked increase in arteriovenous oxygen difference. It appears, then, that once oxygen exchange was again allowed to occur along the upper shoulder of the oxyhemoglobin dissociation curve, that a decrease in hemoglobin-oxygen affinity provided a major advantage in supplying oxygen to the tissues.

Taken together, these two experiments suggest that (1) at non-critical levels of hypoxia, a retention of oxygen by hemoglobin is compensated for by an increase in cardiac output; (2) that when hypoxia is severe, a shift in hemoglobin-oxygen affinity in either direction has no effect; but (3) that upon recovery from severe hypoxic stress, the presence of low affinity blood will be associated with higher levels of available tissue oxygen at less expense of cardiac output.

But to us the most important information to come from these experiments was the conviction that further understanding of the relationship between hemoglobin-oxygen affinity and tissue oxygenation cannot be gained by experiments employing intact animals. This is based on the facts that the influence of shifts in affinity varies with the partial pressure of oxygen, and that the mean partial pressures over which oxygen is released varies from organ to organ and within individual organs. The capacity for hemodynamic compensation also varies, so that there is little chance that the specific role of hemoglobin-oxygen affinity can be clearly identified in any of the general hemodynamic or metabolic responses that are observed.

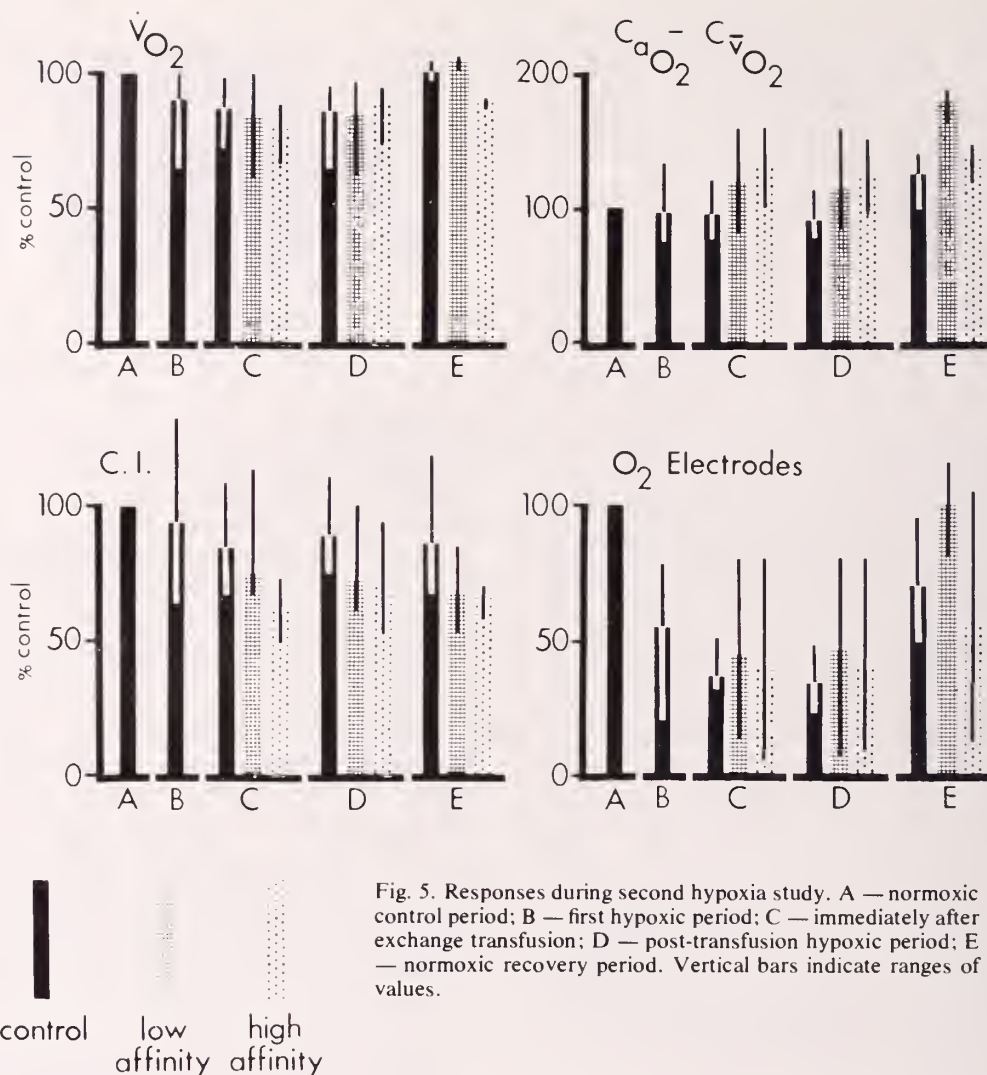


Fig. 5. Responses during second hypoxia study. A — normoxic control period; B — first hypoxic period; C — immediately after exchange transfusion; D — post-transfusion hypoxic period; E — normoxic recovery period. Vertical bars indicate ranges of values.

On the other hand, it remains entirely likely that the tightness with which oxygen is bound by the hemoglobin of circulating red cells is crucial to the function, if not survival, of tissues which have a limited oxygen reserve, particularly if they also suffer from a fixed rate of nutrient blood flow. It is apparent that this description fits the myocardium, but is especially appropriate for the subendocardial layers of the heart with diseased coronary arteries. Since coronary disease remains far and away our number one killer, the need to understand the function of hemoglobin in the compromised heart takes on a new priority. Our current research, which involves the perfusion of isolated rabbit hearts with affinity-modified red cell suspensions, is an attempt to respond to this need.

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Influence of Red Cell Oxygen Affinity and Physical Properties on Oxygen Exchange*

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ABSTRACT

Rates of oxygen uptake and delivery ($\Delta\%$ saturation/ Δt) were determined for isotonic (plasma osmolality = 290 mOsm/kg), hypotonic (240 mOsm/kg), and hypertonic (700 mOsm/kg) blood samples of equal hemoglobin concentration flowing through oxygen-permeable tubing within a gas exchange monitor. $P_{50(7.4)}$ values were 25.0, 23.5, and 28.7 mmHg, respectively. Despite the significant rightward shift in P_{50} , the shrunken, crenated erythrocytes of the hypertonic samples demonstrated an oxygen uptake rate that was initially slower, but predominantly faster than that of the normal biconcave discs of the isotonic (control) samples. Conversely, despite a leftward shift in P_{50} , the swollen red cells of the hypotonic samples delivered oxygen at a faster rate than the normal cells. These results indicate that the physical properties of erythrocyte size, shape, and intracellular hemoglobin concentration, and the related processes of oxygen and oxyhemoglobin diffusion, may have an effect on the actual uptake and delivery of oxygen under non-equilibrium conditions that is as important, or more important, than hemoglobin-oxygen affinity.

facilitated diffusion ionic strength human erythrocytes
intracellular hemoglobin concentration

INTRODUCTION

The importance of hemoglobin-oxygen affinity in the process of tissue oxygenation has been greatly emphasized in recent years. A decrease in oxygen affinity (a rightward shift in the oxyhemoglobin dissociation curve) increases the volume of oxygen released from hemoglobin for a given change in oxygen partial pressure and, therefore, has been considered beneficial in improving tissue oxygenation. However, the actual position of the dissociation curve is usually determined under a standard set of equilibrium conditions and may not accurately reflect the situation in the tissues. In fact, the overall rates of oxygen uptake and release by the erythrocyte are dependent on several additional properties of the red cell such as membrane surface area and oxygen permeability, diffusion distances within the

cell, and intracellular hemoglobin concentration. Although the influence of each of these factors on oxygen transport has been studied individually, their relative roles in determining oxygen exchange rates have not yet been clearly established.

As a focal point for a discussion of these variables, a series of experiments will be described which were designed to compare in vitro oxygen exchange rates in flowing blood samples exposed to an oxygen gradient to the oxygen affinity of the same blood samples determined under equilibrium conditions. Erythrocyte morphology and oxygen affinity were altered in these studies by changes in the plasma osmolality within physiologic (hypertonic renal medulla) or pathologic (hyponatremia) limits.

MATERIALS AND METHODS

All experiments were performed on freshly drawn heparinized blood samples from healthy male volunteers. The initial preparation of all blood samples consisted of centrifugation at 4000 rpm for ten minutes, removal of the buffy coat, and adjustment of the hematocrit to 50 percent. The blood was then divided into three equal portions of 20 ml each. Isotonic (control), hypotonic, and hypertonic samples were produced by adding to each 20 ml aliquot 5 ml of one of the following buffered (33 mEq/L HCO_3^-) solutions: 0.9 percent NaCl, distilled water, or a 1:1 mixture of the original plasma of the sample and a 12.5 percent NaCl solution. Osmolality values for these added solutions were 285, 64, and 4000 mOsm/kg, respectively. The volume of solution added produced a 40 percent hematocrit in the isotonic sample and preserved equal hemoglobin concentrations in all three groups. The solution used to produce the hypertonic samples contained additional plasma to reduce the dilution of plasma proteins and ions by the large amount of water drawn from the cells when this solution was added.

Osmolality (mOsm/kg) was determined by freezing point depression (Fiske Osmometer, Fiske Associates, Hathorne, MA), hematocrit was measured using the microcapillary method, and erythrocytes were counted with a Model F Coulter Counter.

Oxygen Affinity Determinations: The equilibrium oxygen affinity of the samples, expressed as the $P_{50(7.4)}$ (the partial pressure of oxygen in millimeters of mercury which produces 50 percent saturation of the hemoglobin at pH 7.4 and 37° C) was determined using tonometry (Tonometer Bath,

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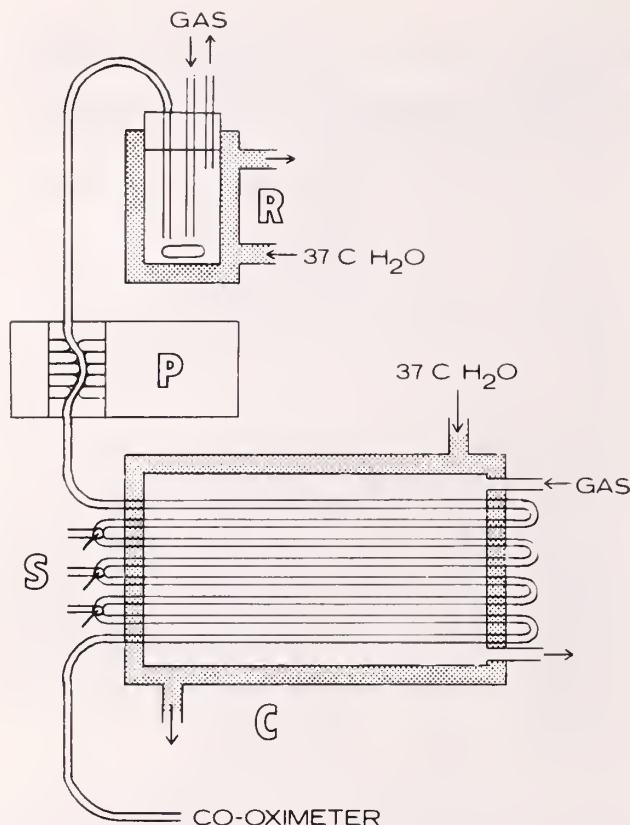


Fig. 1: Gas Exchange Monitor (GEM). From the reservoir (R), where initial equilibration with a known gas mixture is achieved by bubbling and stirring, the blood samples are pumped (P) (Model 500-1200, Harvard Apparatus Co., Dover, MA) through 45-cm lengths of thin-walled silicone rubber tubing (0.058" ID X 0.077" OD, Silastic Medical Grade Tubing, Dow-Corning, Midland, MI) contained within a water-jacketed cylinder (C) perfused with a room air — CO₂ or nitrogen — CO₂ mixture. A system of stopcocks and gas-impermeable tubing allows the blood to flow directly into the CO-oximeter from five equally spaced sampling points (S), only three of which are shown.

Model 137, IL) at 37° C with nitrogen or room air in 5 percent CO₂. Intermediate values for percent saturation were obtained using the mixing technique, and determinations of pH, PO₂, and PCO₂ were made on the mixed samples using a blood gas analyzer system (Models 123, 125A, and 127, IL). Hemoglobin concentration and percent saturation were determined using a CO-oximeter (Model 182, IL). All values for PO₂ were corrected to pH of 7.4 using the Severinghaus nomogram.²⁸

Oxygen Exchange Determinations: Non-equilibrium oxygen uptake and release rates were measured on isotonic, hypotonic, and hypertonic samples flowing through gas-permeable tubes contained within a Gas Exchange Monitor (GEM) shown in Figure 1.

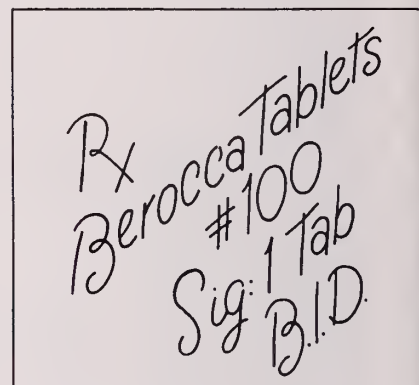
In each experiment, the blood in the reservoir was oxygenated or deoxygenated using room air — 5% CO₂ or nitrogen — 5% CO₂. Following measurement of the initial percent saturation, the sample was pumped through the entire length of the

Continued on Page 16

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X

GEM, which was perfused with nitrogen — 5% CO₂ or room air — 5% CO₂ for oxygen delivery or uptake, respectively. The hemoglobin concentration and percent saturation of the outflow blood were continually measured until stable values were obtained. Duplicate determinations were then made at the outflow and serially from each intermediate stopcock. Each experiment, then, consisted of oxygen uptake and release rate determinations on the control, hypotonic, and hypertonic samples prepared from a single donor.

From the known flow rate and the length of gas-permeable tubing the blood has traversed, the change in percent saturation with time was established. Although the tubing used in the GEM has an internal diameter much greater than that of a tissue capillary, the amount of oxygen released or taken up still depends on the magnitude of the oxygen tension gradient, which in turn depends on the saturation of the blood and the position of the dissociation curve. Also, since the three samples in each study have the same hemoglobin concentration (gm Hb/100 ml blood), the effect of hemoglobin level on exchange is eliminated. The relative rates of oxygen exchange as measured by this device are, therefore, subject to the same influences which determine tissue gas exchange.

RESULTS

Red Cell Indices and Appearance: The sample preparation described above produced isotonic, hypotonic, and hypertonic blood samples with mean plasma osmolality values of 290, 240, and 700 mOsm/kg, respectively. The indices for the cells of the three groups in 20 experiments are shown in Table 1.

The osmotically-induced shift of water across the cell membrane caused a 17 percent increase in the mean cell volume (MCV) in the hypotonic samples and a 32 percent decrease in the hypertonic samples, determined by the changes in the hematocrit and reflected in the mean cell hemoglobin concentration (MCHC). The use of a single donor for each set of samples, as well as equivalent dilutions during the preparation, preserved nearly identical values for mean cell hemoglobin content (MCH), the number of red cells per cubic millimeter, and the total hemoglobin concentration (gm/100 cc).

Microscopically, the cells in the isotonic samples were biconcave discs appearing singly and in short 2-3 cell rouleaux. Slightly swollen erythrocytes with thickened rims and smaller dimples were seen in hypotonic blood, while the hypertonic samples contained crenated cells in both disc and sphere forms, all noticeably smaller than in the isotonic group. No rouleaux were seen in the hypotonic or hypertonic samples.

Oxygen Affinity Studies: The P_{50(7.4)} values (mean ± S.E.M.) for the isotonic, hypotonic, and hypertonic samples were 25.0 ± 0.9, 23.5 ± 1.1, and 28.7 ± 0.7 mmHg, respectively. Reducing plasma os-

TABLE 1
RED CELL INDICES* OF SAMPLE GROUPS

	Hypotonic (n = 20)	Isotonic (n = 20)	Hypertonic (n = 20)
Hematocrit (%)	45.4 ± 0.2	39.5 ± 0.1	26.8 ± 0.3
Hemoglobin (gm/100 cc blood)	14.3 ± 0.2	14.1 ± 0.1	14.1 ± 0.1
Red Cell Number (x 10 ⁶ /mm ³)	4.34 ± 0.1	4.40 ± 0.1	4.2 ± 0.1
Mean Cell Volume (μ ³)	105.5 ± 2.3	89.9 ± 1.9	61.4 ± 1.4
Mean Cell Hemoglobin (μ μ g)	32.4 ± 0.6	31.9 ± 0.7	32.3 ± 0.6
Mean Cell Hemoglobin Concentration (gm/100 cc cells)	31.5 ± 0.4	35.7 ± 0.2	52.1 ± 0.4

*Values given are mean ± S.E.M.

molality, therefore, caused an increase in hemoglobin-oxygen affinity; conversely, increasing plasma osmolality lowered oxygen affinity. Both changes were significant at the p < .025 level.

Oxygen Exchange Studies: The results of 20 oxygen exchange studies are shown in Figures 2 and 3. Figure 2, illustrating the level of percent saturation attained by the three groups at each of the GEM sampling points during 20 oxygen uptake studies, indicates that the hypotonic samples reached higher levels of oxygen saturation than the control samples at each point. The hypertonic samples, on the other hand, demonstrated an unusual pattern of oxygen uptake, in which the percent saturation was significantly lower than the control at point #1, but significantly higher at point #3.

In 20 oxygen release studies, shown in Figure 3, the hypertonic samples reached significantly lower levels of saturation at points #3-6. The hypotonic values were similar to the controls until point #6 where this group was also lower than the control group.

DISCUSSION

P₅₀: The relationship between the shape and position of the oxyhemoglobin dissociation curve and ionic strength is well documented for hemoglobin solutions.^{1,2,6,23,24} A reduction of the salt concentration of the solution produces a less sigmoid curve (a decrease in Hill's number, n*) with a decreased P₅₀. An increase in the salt concentration results in a more sigmoid dissociation curve (because of increased heme-heme interaction) and, in the case of neutral salts, causes an increase in P₅₀.²⁵ The changes in oxygen affinity seen in our experiments and those of other workers³⁴ indicate that this same relationship holds true in intact red cells whose intracellular ionic strength has been altered osmotically.

*Hill's equation $Y/(100-Y) = KP^n$ is an empirical formula which describes the shape of the oxygen dissociation curve, with K = constant, Y = % saturation, P = partial pressure of oxygen, and n = Hill's number.

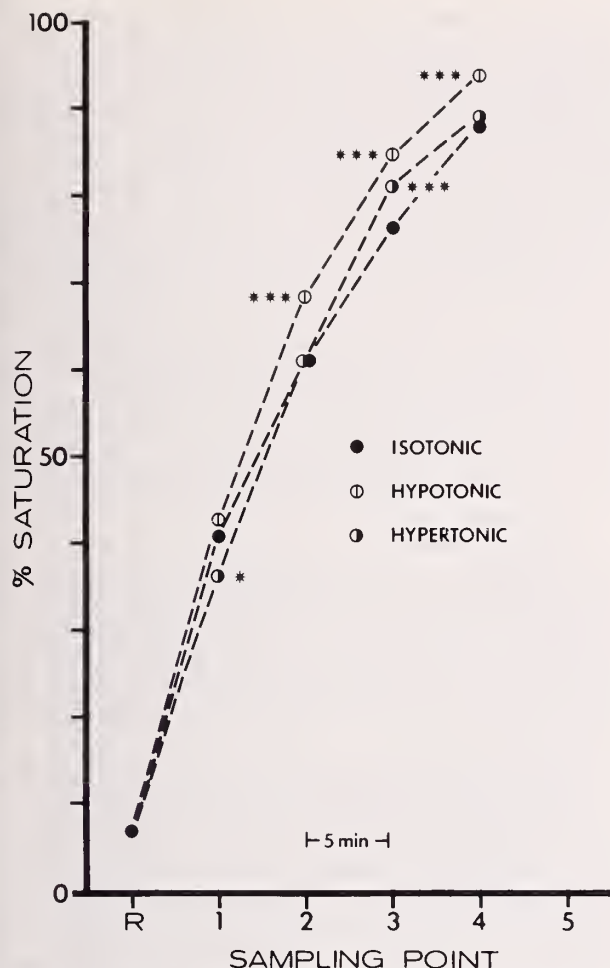


Fig. 2: Oxygen Uptake Studies. The mean values of percent saturation for each sample group at each sampling point are shown for twenty experiments. Significant differences between the hypotonic or hypertonic and the isotonic samples (using the Student "t" test for paired comparisons) are indicated as follows: * = $p < .05$, ** = $p < .025$, *** = $p < .001$.

Such osmotic movements of water across the cell membrane also change the intracellular hemoglobin concentration, which in itself has an effect on the oxygen affinity of the cells^{1,8} perhaps through a lowering of the intracellular pH brought about by the hemoglobin dilution.³ Since the P_{50} changes due to dilution or concentration of intracellular ions and hemoglobin molecules are in the same direction, the contribution of each to the shifts in oxygen affinity observed in our samples is difficult to determine.

The absolute concentration of intracellular organic phosphates, especially 2,3-diphosphoglycerate, which is an important physiological regulator of oxygen affinity, also varied among the three groups, but more importantly, the relative concentrations of these phosphates with respect to hemoglobin were preserved, since all the cells in the three sample groups for a given experiment were from the same individual. Despite maintenance of the 2,3-DPG/Hb ratio, the effectiveness of 2,3-DPG as a modifier of oxygen affinity has been shown to decrease as the concentration of other salts increases.¹

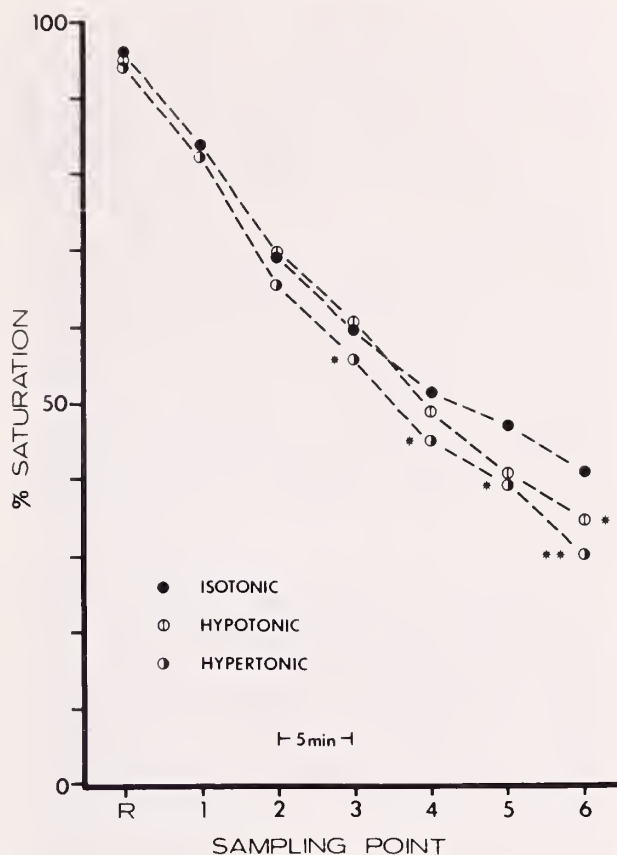


Fig. 3: Oxygen Release Studies. For explanation, see Fig. 1.

The P_{50} values in the present study, then, are the combined result of the interaction of ionic strength and 2,3-DPG and the direct effects of ionic strength itself and hemoglobin dilution.

In contrast to equilibrium oxygen affinity, dynamic oxygen exchange involves many physicochemical factors in the red cell which may influence the rate at which oxygen moves through the cell membrane and interior.

Surface Area: Oxygen diffusion into a red cell will vary with the cell membrane surface area. The influence of the volume increases produced in our experiments on the red cell surface area is relatively small when compared to the much larger increase in volume necessary to significantly stretch the cell membrane.^{21,26,27} Some studies indicate that membrane invaginations resulting from high tangential stresses may persist upon returning to isotonicity from a swollen hypotonic state,¹⁷ but the stress was much more severe than in the present experiments. Similarly, changes in cell morphology produced in osmotic crenation are considered entirely reversible^{9,30} and are consistent with the concept of a simple reduction of cell volume while maintaining a constant surface area.

Membrane Oxygen Permeability: The possibility that the membrane itself may be a limiting factor in oxygen uptake (or release) has been studied by many workers. Generally it has been found that under normal circumstances, the cell membrane has

a finite diffusion resistance^{7,14} which is not rate-limiting^{15,35} and which should be included as part of the total diffusion resistance of cell membrane and contents.¹³ In the face of the relatively minor stresses imposed upon the cells as described above, the red cell membranes in this study can be considered equivalent in terms of their permeability to oxygen.

Intracellular Diffusion and Chemical Reaction Rates: Movement of oxygen in the cell interior involves the simultaneous processes of molecular diffusion and chemical reaction^{11,32} which are both dependent on the oxygen partial pressure gradient and the intracellular hemoglobin concentration.^{5,10,12,22,28,31} Oxygen may also diffuse in the combined form, oxyhemoglobin, and this phenomenon of "facilitated diffusion"¹¹ has been thought to enhance oxygen exchange by as much as 30 percent.¹⁹

Facilitated diffusion, however, requires the presence of an oxyhemoglobin concentration gradient inside the cell, and the rate at which this gradient is established during the initial phase of oxygen uptake (or release) depends on the hemoglobin-oxygen affinity.¹⁸ Also, when equilibrium is approached and all concentration gradients are diminished, facilitated diffusion is much reduced. There exists, then, a maximum effect of oxyhemoglobin diffusion in the intermediate phase of the oxygen exchange process.

As seen in Figure 2, the relative rate of oxygen uptake (determined from the slope of the uptake curve) of the hypotonic and hypertonic samples from 10 percent to roughly 40 percent saturation is in the same direction as the shift in equilibrium hemoglobin-oxygen affinity of the sample. This relationship disappears as the reaction continues, however, and at the level of 80 percent saturation both the hypotonic and hypertonic samples show a more rapid oxygen exchange than the isotonic control. This is contrary to what is expected in terms of oxygen affinity, and can be only partially explained by the process of facilitated diffusion.

In the oxygen release studies, Figure 3, the relation between the relative rate of oxygen delivery and oxygen affinity holds true for hypertonic samples only. At lower levels of saturation both groups showed a greater delivery than the isotonic samples.

Facilitated diffusion may be evident in the hypotonic samples, since both uptake and release rates for this group were approximately 30 percent higher than the control. Previous theoretical and experimental studies^{18,19} have shown a similar degree of acceleration of oxygen exchange. Facilitated diffusion, acting to speed up oxygen exchange in either direction, could possibly, therefore, be playing a greater role in determining the overall rate of oxygen exchange than hemoglobin-oxygen affinity in this instance.

The unusual pattern of oxygen uptake in the

hypertonic samples is more difficult to interpret. The very concentrated hemoglobin inside these crenated cells make facilitated diffusion a very unlikely mechanism, although purely molecular diffusion of oxygen can still occur even in a hemoglobin crystal.²⁰ But the reduced hemoglobin-oxygen affinity of the crenated cells is overcome by some other process or processes which accelerate both oxygen uptake and release to a level in the uptake studies even higher than that of the hypotonic samples.

Gas uptake in the crenated cell has been found previously⁴ to be slower than in normal cells, but these studies used nitric oxide and the uptake process reached only 40 percent NO-hemoglobin. For the corresponding increment of oxygen uptake in our studies, crenated cells also show a slower overall uptake rate.

Diffusion Distance: The increase in volume of the hypotonic cells was accomplished primarily by an increase in thickness and reduction of the size of the dimple. The result is an increase in diffusion distance in these cells, but no effect is apparent, possibly due to the increased diffusivity of oxygen, hemoglobin, and oxyhemoglobin in the more dilute intracellular fluid.

The hypertonic cells were observed to be of both crenated disc and crenated sphere forms in roughly equal numbers. The former, with a decreased thickness, would have a shorter diffusion distance, but these are balanced by an equal number of crenated spheres with a radius of approximately 2.5μ , possessing a greater than normal maximum diffusion distance.

Rheological Properties of Cells: The increased surface area/volume ratio of crenated cells has been suggested as a possible explanation for more rapid oxygen exchange. In a study of oxygen release rates in normal and crenated blood samples at varying shear rates,³⁵ it was found that below a shear rate of 27 sec^{-1} , crenated cells released oxygen slower than normal cells, but above that shear rate, oxygen release was greater than normal. Since membranes of crenated cells have been found to be more deformable than normal cells,²¹ it was postulated that higher shear forces, transferred through the cell membrane,²⁵ caused greater than normal convection and stirring of the contents of crenated cells, contributing to more rapid equilibrium. The wall shear rate in our studies (4 V/r) was 39 sec^{-1} .

Much information exists, however, including unpublished data from this laboratory, which indicates that the higher internal viscosity of crenated cells causes them to be much less deformable than normal cells over a wide range of experimental conditions^{9,26,27,33} making increased convection in these cells an unlikely mechanism.

By the same argument, swollen hypotonic cells would have decreased deformability because of a reduced surface area/volume ratio and the contribution to the overall exchange rate would be in a direc-

tion opposite that seen in these studies.

The rheological interactions of the cells and their suspending mediums are very complex and are in this study very difficult to interpret in terms of their effect on oxygen exchange.

In conclusion, it is evident that the influence of small but significant shifts in hemoglobin-oxygen affinity on the overall rate of oxygen uptake may be masked by the combined effects of changes in the physical aspects of the cell such as size, shape, and intracellular hemoglobin concentration. P_{50} , then, may not always be a reliable indicator of the adequacy of oxygen delivery in disease states where red cell morphology or structure has been altered.

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Happy New Year to all members of the M.M.A.
from the Woman's Auxiliary

Respiratory Variations in the Vectorcardiogram Due to Changes in Thorax Dimensions†

CLIFFORD V. NELSON, Ph.D.* and BRIAN C. HODGKIN, Ph.D.**

Changes in the electrocardiogram of the human being or animal due to respiration are frequently seen. The reduced amplitude with inspiration (Fig. 1) has been ascribed to changes in heart position, greater distance of the heart from the chest wall, increased blood in the right side of the heart and in the lungs due to more negative intrathoracic pressure, and increased electrical resistance of the lungs due to more air.¹ In deep respiration the change in chest circumference is between 5 and 11 cm.² To our knowledge no quantitative studies have been made on effects of changes in thoracic dimensions on the vectorcardiogram (VCG), mainly because no good method for doing this has existed. We have developed a vector lead system which can be adjusted for thorax dimensions.³ By adjusting the system for dimensions at expiration, recording VCGs, and then readjusting for inspiratory dimensions and repeating the measurements, we have been able to eliminate the effects of dimensional changes. Using VCG values at expiration as a base, changes with inspiration were quite different from the uncorrected values. In some cases the peak vector magnitude increased with expiration rather than decreasing.

The lead system³ uses three rows of eight electrodes around the thorax for the X (left-right) and Z (posterior-anterior) leads. Potentiometers are used to adjust for the size and shape of the thorax. The Y (vertical) lead is obtained from electrodes on the left leg and neck. The system is applicable to animals as well as human beings. The equations used are as follows:

$$M_x = G_x k HP V_x \quad (1)$$

$$M_y = kAV_y = T k HP V_y \quad (2)$$

$$M_z = G_z k HP V_z \quad (3)$$

$$M = \sqrt{M_x^2 + M_y^2 + M_z^2} \quad (4)$$

$$H^\circ = \tan^{-1} \frac{M_z}{M_x} \quad (5)$$

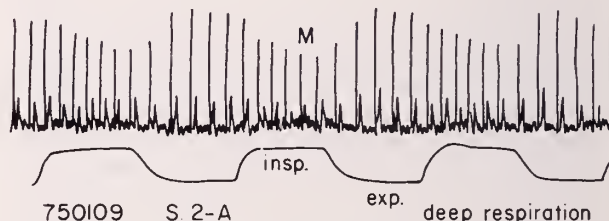


Fig. 1. Analog computer record of peak vector magnitude during deep respiration. Each vertical spike represents the spatial dipole moment, M (k mA-cm), during QRS or ventricular depolarization. The shorter deflections correspond to T waves. The respiration record was obtained from a thermistor in a plastic tube inserted in the nostril. The M_x , M_y , and M_z signals recorded with the Nelson lead system were applied to the computer. The lead system was adjusted for thorax dimensions at end-expiration and the records are, therefore, not corrected for changes in thorax dimensions.

$$V^\circ = \sin^{-1} \frac{M_y}{M} \quad (6)$$

V° is the angle between M and the horizontal plane, positive values clockwise or inferior, range $\pm 90^\circ$. H° is the angle between the projection of M on the horizontal plane and the $+X$ axis, positive values counterclockwise or posterior, range $\pm 180^\circ$. Positive directions of X , Y , and Z are to the left, inferior (caudad), and posterior, respectively.

In equation 1, M_x is the X component of the heart dipole moment, G_x is a factor used to compensate for the attenuation of the resistance network (read from a table), k is average thorax conductivity, H and P are vertical height and circumference of the thorax, respectively, and V_x is the X output voltage of the lead system.

In equation 2, A is the cross-sectional area of the thorax. The factor $T = \frac{A}{HP}$ is used so that equation 2 can be expressed in the same format as equations 1 and 3. Equations 4 to 6 give the vector spatial magnitude and two angles which define its direction.

It is seen that V_x and V_z are multiplied by thoracic surface area and V_y is multiplied by the cross-sectional area. With inspiration, both surface and cross-sectional areas increase but generally not by the same amounts. These larger area values compensate for the reduced voltages caused by the increased distance of the heart from the body-surface electrodes.

Voltages V_x , V_y , and V_z from the resistance network were amplified and applied to three channels

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of a magnetic tape recorder and to an analog computer. The computer output voltages, proportional to M , H° , and V° , were applied to three more channels of the tape recorder. A respiration signal was recorded on the seventh channel. All records were later replayed onto a direct-writing 7 channel recorder.

When expanded, curves of M had one to three peaks: M_1 corresponding to septal excitation, M_2 to excitation of the free walls of both ventricles, and M_3 to excitation of the basal portions of left ventricle and septum. Table 1 shows the effects of deep respiration in a normal individual. M_2 dropped from 778 to 596 k mA-cm with inspiration but when corrections were made for the changes in thorax dimensions, M_2 was found to be unchanged. M_x+ , M_y+ , and M_z- were the components of M_2 . M_x+ and M_y+ increased but M_z- decreased slightly, showing that there was some rotation of the heart. M_3 and its Z component M_z+ showed increases with inspiration but still larger increases when corrected dimensions were used. Table 1 shows that HP increased by 8.0% but A increased by 23.8% over expiration values.

In another individual, deep inspiration caused a small drop in M_1 , a small increase in M_2 , and no change in M_3 . When corrections were made for inspiratory thorax dimensions, however, M_1 doubled and M_2 and M_3 increased by 26% and 35%, respectively, over values for deep expiration. In two other subjects, normal respiration caused smaller changes than was the case for deep respiration. In the four subjects studied (young adult males), M_1 and M_3 increased in all cases. M_2 increased in two cases, remained unchanged in one, and decreased in the fourth. Fig. 1 shows the uncorrected variation of M_2 which is the peak vector in normal subjects. Without correction, M_2 decreased in all cases. The changes in angles H° and V° were small, indicating that rotation of the heart was not a major factor. Recently, Hashida, *et al* pointed out the importance of changes of chest dimensions in the ECG of athletes.⁴

Since M is essentially independent of heart position, changes remaining after correction for thorax dimensions must be due to other factors such as the air in the lungs or altered blood volumes in the cardiac and pulmonary systems. Since the M_1 and M_3 vectors are usually pointed towards the anterior and posterior, respectively, increased lung resistance would tend to channel the ECG currents towards these surfaces increasing the voltages.⁵ The normal M_2 vector is pointed toward the left and somewhat downwards into the mass of the lungs. Increased lung resistance should, therefore, shield currents from this vector and one would expect the voltages to be reduced. Increased intracardiac

TABLE 1

EXPERIMENT 750109. EFFECTS OF DEEP RESPIRATION ON VECTOR QUANTITIES AND THORAX DIMENSIONS			
Quantity	Exp.	Insp.	Insp. Corrected
M_2	778	596	776
M_x+	357	306	381
M_y+	604	529	699
M_z-	-487	-395	-479
M_3	276	339	370
M_z+	214	304	320
HP	3624	3913	
A	382	473	

blood in the right side of the heart should increase the M_1 and M_2 radially-directed vectors because of the "Brody effect."⁶ A reduced blood volume in the left ventricle would tend to reduce the left ventricular component of M_2 but should increase the tangentially-directed M_3 vector. The effects of respiration on the M_2 vector would, therefore, depend on the relative volumes of air and blood in the lungs and blood in the heart at a given time. Increased blood and air in the lungs would have opposing effects on lung electrical conductivity. By correcting for thorax dimensional changes in respiration, one of the causes of respiratory VCG changes can be eliminated.

SUMMARY

During inspiration, electrocardiographic potentials on the chest wall usually decrease partly because of the greater distance between the heart and the electrodes. By using a lead system which takes thorax dimensions into account, variations due to this cause can be eliminated. In normal objects, peak vector magnitude at about the middle of QRS increased or stayed the same in three or four cases when corrections were made for changes in thorax dimensions. During early and late portions of ventricular depolarization, surface potentials increased with inspiration in all cases.

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Maine Blue Cross and Blue Shield News

EXPANDED HOSPITAL OUTPATIENT LABORATORY BENEFITS

Expanded hospital outpatient laboratory benefits are now a permanent part of Maine Blue Cross and Blue Shield health coverage. This came as a result of a Maine Blue Cross and Blue Shield Board vote on one of several important agenda items recently.

The outpatient program which had been run on a pilot basis for one year, covers tests done in the hospital outpatient laboratory with evidence of illness or injury. A year-end study of the pilot program was made and the Health Care Planning and Research Department of Maine Blue Cross and Blue Shield showed that program objectives of subscriber satisfaction and reasonable cost had been met.

It was the original intent in expanding outpatient benefits to provide coverage for as many outpatient services as possible to help relieve unnecessary use of acute care facilities and save patient's time and money. The utilization rate of hospital beds is the lowest in recent Maine history and, while this fact cannot be conclusively linked to expanded outpatient benefits, Maine Blue Cross staff feels that it may have had some effect. The number of outpatient claims covered by Maine Blue Cross and Blue Shield has increased dramatically, and this does indicate subscriber acceptance of the program.

It was also decided that the Coordinated Home Health Care Pilot Program, which has been in effect since 1972, would be continued on a pilot basis for two more years, or until sufficient statistical information is available to consider making the program a permanent benefit.

All present and potential contracting home health agencies will be required to participate in a formal assessment of their willingness and capability to carry out program responsibilities as outlined by Maine Blue Cross and Blue Shield. Criteria suggested by community committees in Cumberland County, as well as the Ad Hoc Evaluation Committee in Androscoggin and Aroostook Counties, will be an important part of the assessment.

News, Notes and Announcements

State of Maine Department of Health and Welfare Division of Child Health Clinic Schedule — 1976

Orthopedic Clinics

Bangor — St. Joseph Hospital
9:00 a.m.: Jan. 22, Feb. 26, Mar. 25, Apr. 22, May 27, June 24, July 22, Aug. 26, Sept. 23, Oct. 28, Nov. 18, Dec. 23
Fort Kent — Northern Maine Medical Center
9:00 a.m.: Mar. 9, May 11, July 13, Sept. 14, Nov. 9
Houlton — Houlton Regional Hospital
10:00 a.m.: Mar. 8, May 10, July 12, Sept. 13, Nov. 8
Lewiston — Central Maine General Hospital
9:00 a.m.: Feb. 20, Mar. 19, Apr. 16, May 21, June 18, July 16, Aug. 20, Sept. 17, Oct. 15, Nov. 19, Dec. 17
Presque Isle — A. R. Gould Memorial Hospital
9:00 a.m.: Mar. 10, May 12, July 14, Sept. 15, Nov. 10
Waterville — Mid-Maine Medical Center, Thayer Unit
(Time scheduled by hospital): Feb. 2, Mar. 1, Apr. 5, May 3, June 7, Sept. 13, Oct. 4, Nov. 1, Dec. 6

Cleft Palate Clinic

Portland — Maine Medical Center
9:00 a.m.: Feb. 9, May 17, Sept. 20, Nov. 15

Cardiac Clinics

Bangor — St. Joseph Hospital
9:00 a.m.: Feb. 13, Mar. 12, Apr. 9, May 14, June 11, July 9, Aug. 13, Sept. 10, Oct. 8, Nov. 12, Dec. 10
Portland — Maine Medical Center
9:00 a.m.: Jan. 23, 30, Feb. 6, 13, 20, 27, Mar. 5, 12, 19, 26, Apr. 2, 9, 16, 23, 30, May 7, 14, 21, 28, June 4, 11, 18, 25, July 2, 9, 16, 23, 30, Aug. 6, 13, 20, 27, Sept. 3, 10, 17, 24, Oct. 1, 8, 15, 22, 29, Nov. 5, 12, 19, Dec. 3, 10, 17, 31

Children's Development Clinics

Lewiston — Central Maine General Hospital
8:30 a.m.: Jan. 26, Feb. 23, Mar. 8, 22, Apr. 12, 26, May 10, June 14, 28, July 12, 26, Aug. 9, 23, Sept. 13, 27, Oct. 25, Nov. 8, 22, Dec. 13, 27
Waterville — Mid-Maine Medical Center, Thayer Unit
8:30 a.m.: Jan. 21, Feb. 4, 18, Mar. 3, 17, 31, Apr. 7, 21, May 5, 19, June 2, 16, 30, July 7, 21, Aug. 4, 18, Sept. 1, 15, 29, Oct. 6, 20, Nov. 3, 17, Dec. 1, 15, 29

Cystic Fibrosis Clinics

Bangor — St. Joseph Hospital
(Time scheduled by hospital): Jan. 20, Feb. 17, Mar. 16, Apr. 20, May 18, June 15, July 20, Aug. 17, Sept. 21, Oct. 19, Nov. 16, Dec. 21
Lewiston — Central Maine General Hospital
(Time scheduled by hospital): Feb. 6, Mar. 5, Apr. 2, May 7, June 4, July 2, Aug. 6, Sept. 3, Oct. 1, Nov. 5, Dec. 3
Portland — Maine Medical Center
(Time scheduled by hospital): Jan. 20, Feb. 17, Mar. 16, Apr. 20, May 18, June 15, July 20, Aug. 17, Sept. 21, Oct. 19, Nov. 16, Dec. 21

Second Annual Maine Biomedical Science Symposium

The Second Annual Maine Biomedical Science Symposium will be held at the University of Maine at Orono, July 8-10, 1976. Like its successful predecessor, this symposium will provide a common forum for Maine clinicians, biomedical scientists, and educators to *present new advances in their respective fields, to report on research projects, to explain new methods, and to establish greater communication within the biomedical community in Maine.*

The topics of the sessions in the 1976 symposium will be governed by the willingness of people in the State to come forward to chair a given session, solicit papers, and work with us to obtain financial support. This will insure a group of session topics

of particular interest and pertinence to biomedical science in Maine. The sessions for the 1976 symposium will include:

- Genetic Diseases
- Cardiovascular Physiology
- Marine Science
- Cancer
- Aging
- Neurophysiology

Each session will be introduced by a general lecture by a distinguished worker in the field designed to provide an overview of the state of the art in that field.

In addition to regular session presentations, there will be one evening session of poster-presentations on any topic. The informal give and take dialogue characteristic of poster presentations will augment the more formal seminar sessions.

The success of the 1975 symposium demonstrated the great need and desire for greater communication between scientists and clinicians in Maine. Let us build upon the first symposium by making the second symposium even better.

If you wish to present a paper, participate in the planning of the symposium, develop a new session, or assist in obtaining financial support, please contact either Dr. Richard Blake or Dr. David Page.

Richard D. Blake
Dept. of Biochemistry
University of Maine
Orono, Maine 04473
207-581-7149

David S. Page
Dept. of Chemistry
Bowdoin College
Brunswick, Maine 04011
207-725-8731, Ext. 602

1976 Indy '500' Symposium

Postgraduate course in emergency medicine and emergency medical services

Presented by ACEP/EDNA* Indiana Chapters
May 12-15, 1976

Indianapolis Airport Hilton, Indianapolis, Indiana
Fees: EDNA Members \$40.00

EDNA Non-Members \$50.00

ACEP Members \$60.00

ACEP Non-Members \$80.00

Contact: Martin Graber, M.D., 3910 Dundee Drive, Indianapolis, Indiana 46227.

*ACEP — American College of Emergency Physicians
EDNA — Emergency Department Nurses Association

Pre-Natal Testing For Neural Tube Defects

Radioimmunoassay for alpha-fetoprotein in amniotic fluid of women at high risk of bearing a child with a neural tube defect (anencephaly or spina bifida) is now available on a Statewide basis in Maine. This service would be of benefit primarily to women no later than sixteen weeks pregnant who have a positive family history of neural tube defects.

Amniotic fluid and serum sample mailers will be sent on request, and further information can be obtained by contacting: Edward M. Klosa, Project Co-ordinator, Meningomyelocele Project, Rheumatic Disease Laboratory, Maine Medical Center, 22 Bramhall Street, Portland, Maine 04102. Tel.: (207) 871-2627.

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MAINE MEDICAL CENTER
Portland, Maine

MEETINGS AND CONFERENCES — 1976

Douglas W. Walker, M.D.
 Medical Director

Albert Aranson, M.D.
 Director of Medical Education
CHAIRMAN

<i>TIME</i>	<i>MEETING</i>	<i>PLACE</i>	
MONDAY			
Weekly			
7:00 A.M.	Obstetrics-Gynecology Conference	Cafeteria Conference Room C	Dr. R. Lorimer
9:00	Medical Rehabilitation Staff Conference	R4 Conference Room	Dr. J. Lorentz
12:30 P.M.	Ambulatory Pediatrics	Cafeteria Conference Room C	Dr. G. Hallett
2:30	Clinical Anesthesia Lecture	Anesthesia Office	Dr. H. Sawyer
4:00	Cardiac Catheterization Conference	R8 Conference Room	Dr. H. Osher
4:00	Surgical Pathology Review	Pathology Conference Room	Dr. J. Stocks
5:00	Radiology Journal Club	PIC Conference Room	Dr. J. Gibbons
7:00	Dental Treatment Planning Conference	Rolland Irish Classroom #2	Dr. R. Sbrilla & Dr. L. Wolfe
<i>First and Third</i>			
11:00 A.M.	Clinical Nephrology Conference	R5 Nephrology Office	Dr. J. Drewry
12:00 Noon	Hematology-Pathology Conference	Pathology Conference Room	Dr. J. Fanning
<i>Second and Fourth</i>			
11:00 A.M.	Renal Biopsy Conference	Pathology Conference Room	Dr. J. Drewry & J. Stocks
12:00 Noon	Pulmonary Conference	Rolland Irish Classroom #2	Dr. P. Cox
<i>Third</i>			
11:45 A.M.	Eye Conference	Cafeteria Conference Room B	Dr. R. Goduti
TUESDAY			
Weekly			
7:00 A.M.	Radiology Resident's Seminar	Radiology Department	Dr. J. Gibbons
7:30	Dental Journal Club	Doctors Dining Room	Dr. R. Overgaard
9:00	Orthopedic Conference	Orthopedic Clinic	Dr. L. Crane
9:30	Student Technologists Conference	Pathology Conference Room	Dr. J. Stocks
11:00	Psychiatric Conference	NDF Classrooms #3-4	Dr. A. Elkins
11:00	Medical Mortality Conference	Pathology Conference Room	Dr. J. Stocks
12:30 P.M.	ECG Interpretation	Room 9 — R8	Dr. R. Martin
2:30	Anesthesia Basic Science Lecture	Anesthesia Office	Dr. H. Sawyer
4:00	Pathology Slide Seminar	Pathology Conference Room	Dr. J. Stocks
TUESDAY			
<i>First and Third</i>			
12:00 Noon	Radiology-Pathology Conference	Pathology Conference Room	Dr. J. Stocks & J. Gibbons
WEDNESDAY			
Weekly			
7:00 A.M.	Radiation Therapy Conference	Radiology Department	Dr. J.H. Hannemann
7:00	Urology Conference	Richards 5 Conference Room	Dr. F. Clark
9:00	Medical Conference	NDF Classrooms #3-4	Dr. A. Aranson
9:00	Medical Rehabilitation Staff Conf.	R4 Conference Room	Dr. J. Lorentz
12:00 Noon	Medical Residents Conference	Cafeteria Conference Room B	Dr. A. Aranson
3:00 P.M.	Surgical M&M and Grand Rounds	Doctors Dining Room	Dr. R. Britton
<i>First and Third</i>			
12:00 Noon	Radiology-Pathology Conference	Pathology Conference Room	Dr. J. Stocks & J. Gibbons
2:30 P.M.	Anesthesia Complication Conference	Anesthesia Office	Dr. H. Sawyer
<i>Second</i>			
9:00 A.M.	Guest Internist — Medicine	NDF Classrooms #3-4	Dr. A. Aranson
<i>Second and Fourth</i>			
12:00 Noon	General Radiology Seminar	Radiology Conference Library	Dr. J. Gibbons
2:30 P.M.	Anesthesia Journal Club	Anesthesia Office	Dr. H. Sawyer
<i>Fourth</i>			
9:00 A.M.	Medical Mortality Conference	NDF Classrooms #3-4	Dr. A. Aranson

<i>Alternate</i> 11:00 A.M.	Neurology-Psychiatry Seminar	P6 Day Room	Dr. E.C. Kunkle
THURSDAY			
<i>Weekly</i> 7:00 A.M.	Diagnostic Radiology Teaching Conf.	Radiology Department	Dr. J. Gibbons
8:00	Surgical Conference	NDF Classrooms #3-4	Dr. R. Britton
9:00	Pediatric Conference	Rolland Irish Classroom #2	Dr. G. Hallett
11:00	Tumor Consultation Board	Radiation Therapy Conf. Library	Dr. R. Carroll
5:00 P.M.	Endocrinology Conference	Research Library	Dr. H. Johnston
THURSDAY			
<i>First</i> 9:00 A.M.	Guest Pediatrician	NDF Classrooms #3-4	Dr. G. Hallett
<i>First and Third</i> 12:30 P.M.	Cardiology-Surgical Conference	R8 Conference Room	Dr. C. Lutes
<i>Second and Fourth</i> 1:15 P.M.	Pediatric Psychiatry	Pediatric Conference Room	Dr. R. Levy
<i>Second, Fourth and Fifth</i> 12:30 P.M.	Cardiology Teaching Conference	R8 Conference Room	Dr. H. Osher
<i>Second</i> 5:30 P.M.	Eye Staff Scientific Session	PIC Conference Room	Dr. R. Goduti
6:00	Maine Medical Center Medical Staff Meeting and Scientific Session	NDF Classrooms #3-4	Dr. G. Sager
<i>Third</i> 9:00 A.M.	Combined Guest Physician Programs or Guest Surgeon	NDF Classrooms #3-4	Dr. R. Britton
2:30 P.M.	Anesthesiology Report of Clinical Meetings	Anesthesia Office	Dr. H. Sawyer
<i>Fourth</i> 8:00 A.M.	Surgical Mortality Conference	NDF Classrooms #3-4	Dr. R. Britton
<i>Last</i> 9:00 A.M.	Pediatric Mortality Conference	Rolland Irish Classroom #2	Dr. G. Hallett
2:30 P.M.	Anesthesia Mortality Conference	Anesthesia Office	Dr. H. Sawyer
FRIDAY			
<i>Weekly</i> 7:00 A.M.	Thoracic Surgical Conference	Cafeteria Conference Room C	Dr. E. Drake
7:00	Nuclear Medicine Conference	Radiology Department	Dr. R.C. Briggs
8:30	Neurology-Neurosurgery Conference	Doctors Dining Room	Dr. R. Bidwell
9:00	G.I. Conference	Rolland Irish Classroom #2	Dr. L. Leiter
9:00	Medical Rehabilitation Staff Conf.	R4 Conference Room	Dr. J. Lorentz
<i>Third</i> 12:00 Noon	Oncology Conference	Clinical Conference Room	Dr. R. Carroll
FRIDAY			
<i>Alternate</i> 10:00 A.M.	G.I. Conference — Formal Lecture	Rolland Irish Classroom #2	Dr. L. Leiter
<i>Monday-Friday</i> 4:00 P.M.	Surgical Seminar	Doctors Dining Room	Dr. R. Britton

Reminder to M.M.A. Members

CONTINUING MEDICAL EDUCATION ACTIVITY REPORT

The bylaws of the Maine Medical Association were amended in June of 1973 as follows: Chapter I, Section 11, — "Each member of the Maine Medical Association shall be required to report his activities in continuing medical education every year according to a format provided by the Committee on Continuing Medical Education."

Only active, dues-paying members are required to report this year.

Please fill in your activity report promptly and return to the M.M.A. office, P.O. Box 250, Brunswick, Maine 04011.

Letters to the Editor

To the Editor:

In the regular session of the 107th Legislature, an act amending the law relating to the hospitalization of the mentally ill was passed and became Chapter 559 of the Public Laws of the 107th Legislature.

The amendments were introduced because of problems created by a prior amendment which required an individual who was not suicidal or homicidal to be hospitalized in the in-patient unit closest to his home unless it was impossible to care for him in that unit. That provision meant that an individual had to be cleared by each in-patient unit that was closer to his home than the State hospital and caused unnecessary delays and complications in admission. Such patients — who are mentally ill and are dangerous to themselves but not suicidal or homicidal — can now be hospitalized directly at the State hospital on an emergency basis and then are subject to the usual court procedure which must be initiated within five days of that admission.

Another provision of this amending law requires that at the time of hearing for court commitment, in-patient hospitalization has to be demonstrated to be the most appropriate treatment for the patient, and an individualized treatment plan must be explained to the judge who then makes the decision about involuntary commitment of the patient as providing for the most appropriate treatment.

In the implementation of this law, we prepared some new forms which were on an orange-colored sheet and distributed these to all mental health centers, all general hospitals, police departments and sheriff departments but we did not make a general mailing to all physicians because of a departmental policy that patients to be admitted to state hospitals should be first cleared through their respective mental health centers. This pol-

icy is consistent with the requirement that in-patient hospitalization must be the most appropriate treatment for the patient in order for the patient to be court committed. The resources, short of hospitalization, usually are located in the mental health centers.

At this time of fiscal constraints in governmental operation, you can well understand that we were loath to send out a large mailing of almost fifteen hundred, including the postage and printing cost of additional forms which most physicians would not use. These forms, however, are available on request to this Department or through the local mental health centers. We would be very happy to forward copies of the new forms and the explanation of the changes in the statutes to anyone requesting them.

Incidentally, Doctor Hanley, our goal of having all patients being admitted to the mental health institutes cleared by the local mental health center is pretty close to realization. Our rates are from 85-93% in the various center areas, and the number of inappropriate admissions or admissions which could be forestalled by other treatment resources, such as day treatment or halfway houses, has been markedly reduced.

Again, may I say that there was no intention on the part of this Department to ignore physicians' needs. We will gladly send a supply of forms to anyone requesting them. Just mail or call a request to: Department of Mental Health & Corrections, Bureau of Mental Health, 411 State Office Building, Augusta, Maine 04330. Tel.: 289-3161.

WILLIAM E. SCHUMACHER, M.D.
Director
Bureau of Mental Health

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The Journal of the Maine Medical Association

Volume Sixty-seven

Brunswick, Maine, February 1976

Number 2

SAFETY for the C.V.A. PERSON on GOING to the HEAD!

A Case Report from Rehabilitation Medicine

LEROY J. WALTON, ELAINE STEVENS, M.A., C.C.C. and
RICHARD T. CHAMBERLIN, M.D., F.A.C.P.

"I am a fifty-nine-year-old male who has had a C.V.A. or "cerebral vascular accident" resulting in the complete paralysis of entire right side of the body — with loss of speech, i.e., a stroke. For those of you who know a person in this situation who

and those of you might come in contact with such a situation, here are some helpful safety hints.

"The paralysis of the entire right side of body means outside (skin) and inside! For instance; half of bowels you can feel as well as you did before the stroke but the other half of the bowel on the paralysed side you can't feel — nothing. The kidneys and the urinary bladder are the same — half and half. So the first thing you have to know, is when you have to GO. Might be better to start to the Head before you ever get wind of it. A right smart safety precaution!

"How to help? By not asking a "physically handicapped" person any questions, such as, "Where are you going?" Now with cane, and trouble with the stairs, and getting out of the chair, it is bad enough to get there in time without having to answer any ~~xxx~~ questions — with very little speech.

"The safety-conscious person will know the proper way to approach the Head — with it to the rear of you. It doesn't matter what you THINK you have to do, it's always best ~~x~~ to sit down — just in case. (Editor's note: Females don't have that problem.) An unassisted handicapped person can or must be cautious by not wearing suspenders because they always get wet and slimy. It is bad enough to unzip your fly, loosen the belt, pull down the underpant, pull up the shirt and undershirt with the only good hand without trying to get the suspender strap from out of the water. And one-piece underwear is impossible.

"Now there is one complicated aspect of safety ~~of safety~~ in sitting down. It is to be remembered when you are standing, you balance on both legs but when you are bending at the knees, you lose the support of the paralysed leg. Don't miss the Head! To miss brings on the strain — too much! For when you do stand up again, you need a bath — and that's another story. Don't cry out for assistance for you are too excited for unstandable speech.

"Observing safety rules is equally important for the non-
as

handicapped person as well as the handicapped. If a non-handicapped person did not follow safety rules pertaining to him, he would have accidents just as easily as a physically handicapped would. Once he is sitting down, it is not good to have the person

ring or the door bell ring, or the wife saying, "Look at the petty girls swimming on T.V.!" When it comes time for you to get up, you don't find it that simple. First, with the one good hand you got to tear off a piece of toilet tissue from the roll — worse if it's just down to one-third of a roll. Not safe but use your teeth for another hand.

"Now, to use the toilet paper you must sit on the seat half-ass. Again women don't have this situation. The bad part of this half-ass position is that you got to get your paralysed cheek to hold all the rest of your body while you one-handed do your chore and balance yourself. Balance? Slipping one way could result ending up on the floor with your good hand in the bowl — again you get to take a bath. Did you ever try to ~~xxxx~~ scrub your arm with the hand on the same arm — you don't have a second arm to help out?

"All good things must come to the end! It is time to stand up and dress-up. Stand up? With the right side of your body paralysed you have to raise yourself with one leg — from sitting below chair's level. After finally arising, try to buckle your belt — one-handed! And pull up your zipper — one-handed!

"All of that for a little old fart — now that's safety. It's best not to take a chance."

THE PATIENT IS "SPEAKING" — ARE WE LISTENING?

The practice of medicine has the potential of being a most rewarding educational experience for all people on the health care team if they will but allow it to happen. The author of the opening story is a patient who is recovering from a stroke. He typed the story himself about nine months after he suffered his stroke. He provides an exceptionally good example of the dictum "Listen to the patient, he is telling you the diagnosis."² The case also provides an opportunity to review and update the problem of Oral Apraxia as well as to relate speech therapy to the rehabilitation processes of continuing care.

CASE REPORT

The case report will consist of several sections: (1) The standard medical descriptive report, (2) the continuing care section stressing team evaluation and discharge planning, and (3) follow-up — "The Patient Speaks."

STANDARD MEDICAL DESCRIPTIVE REPORT

A 59-year-old white, married male self-employed leatherer

was transferred to the Thayer Unit of the Mid-Maine Medical Center on 24 December 1974 for rehabilitation. There was a history of diabetes mellitus controlled by diet and oral hypoglycemic agents since 1967 and of hypertension of unknown degree over the same period of time. During the six months prior to admission, he had an episode of dyspnea and signs of pulmonary congestion. Although he had responded to diuretic therapy with a weight loss of forty pounds, his activity was still limited by dyspnea. On 3 December 1974, he was found lying on the floor unresponsive. Upon admission to a hospital, he was barely responsive to painful stimuli. Temperature 98.6. Pulse 100. Respiration 20. Blood Pressure 150 over 70. The skin over the distal lower extremities was smooth and shiny, lacking hair. The eye-grounds did not show either hypertensive or diabetic retinopathy. There were no bruit in the neck and the carotid pulses were of good quality and equal. The chest was normal in configuration and was clear to auscultation. The heart was not enlarged to percussion and the cardiac rhythm and sounds were normal. The abdomen was moderately obese. The liver edge was palpable 2 cm. below the right costal margin. Rectal examination was normal. The extremities were normal with good peripheral pulses. Neurological examination revealed a semicomatose man with an obvious flaccid paralysis involving the lower right side of face, and both upper and lower right extremities. There were no deep tendon reflexes on the right. The Babinski response was extensor on the right.

Laboratory examinations included a normal CBC, urinalysis and electrolytes. The initial blood sugar was 239 mg. percent. Chest x-ray revealed slight increase in transverse diameter of the heart and slight pulmonary congestion. EKG showed non-specific T-wave changes. Brain scan demonstrated increased uptake over the left middle cerebral hemisphere and EEG showed focal slowing with delta waves in the corresponding area. Lumbar puncture showed normal pressures, no cells, and normal protein. The initial working impression was stroke syndrome with right hemiparesis, possibly secondary to cerebral embolus, diabetes mellitus, hypertension and mild congestive heart failure.

Therapy included bed rest with supportive intravenous fluid replacement. Corticosteroids were used initially and anticoagulation was begun. The blood sugar was controlled with insulin and it was necessary to start indwelling catheter drainage of the urinary bladder due to urinary retention. Physical therapy evaluation on the third hospital day detected no muscle tone on the right and a program of passive range of motion of all joints and frequent careful positioning was begun.

During the first week in the hospital, the patient became more responsive and it became clear that he had an expressive aphasia with some difficulty in swallowing. At seven days, re-evaluation revealed some return of muscle tone with slight volitional motion at the right shoulder and proximal right leg and hip. Progressive sitting up with assistance revealed a rapidly improving sitting balance. By fourteen days, he had progressed through difficult transfer activity with two assists to easy transfer with minimal assist. By the end of the third week, the difficulty with swallowing improved enough to allow normal eating and transfer activities were nearly independent. He was able to walk between parallel bars with external stabilization of the right ankle. Speech was still severely involved and he was transferred for further rehabilitation evaluation and continuing care.

CONTINUING CARE

Following transfer to the Continuing Care Ward of the Thayer Unit of the Mid-Maine Medical Center and the recording of the previously documented medical information, a careful patient profile was obtained. The confidential nature of some of this information is protected in this report but the purpose of gathering the information was to obtain as clear a picture of the pre-morbid nature of the patient as was possible in order to assist the process of setting rehabilitation goals and for discharge planning. The patient had retired from business in New Jersey before moving to Maine. The family group included he and his wife who worked regularly outside of the home and wished to continue working if at all possible. The patient had developed an active

business of leather crafting which he operated from his own home. He was a meticulous worker with a well developed schedule. He maintained control of all the family financial affairs and planning. There had been some difficulty in the ease of communication and of inter-personal relationships in the year before his stroke. It was clear that to set a goal of anything less than a fairly independent existence in a home care setting for the patient would present definite serious adjustment problems for him. It was clear that he understood and eagerly wanted to learn more about the nature of his disability and that he would carefully carry out all suggestions and programs for his rehabilitation.

As his continuing care program progressed to the point that trial visits to his home on weekends became possible, it was also clear that given the fact that his muscle strength and coordination for walking was improving, and although there was little or no return of function of the right upper extremity, his speech handicap presented for him the single most serious disability in relation to his future adaptation. Therefore, his continuing care program became centered strongly on his speech therapy program while physical therapy and occupational therapy continued to improve the muscular weakness and coordination of his right side. The entire continuing care program was monitored by continuing care team conferences which were held every 7 to 10 days with the physician, nurse, physical therapist, occupational therapist, speech therapist, and social worker in attendance. Notes and recommendations from these conferences were entered into the patient's medical record and discussed with the patient and his family. Progress of the patient following discharge to a home care program was also followed and documented in Team Conferences.

The patient gained virtually independent status in regards to activities of daily living and was discharged to a home care program which included outpatient physical and speech therapy. That the goals of his continuing care program have been reached, may be best demonstrated by the opening section of this article. This material was sent to those who had cared for him by the patient himself and is reproduced exactly as it was received from him having been typed by the patient with his good left arm and hand.

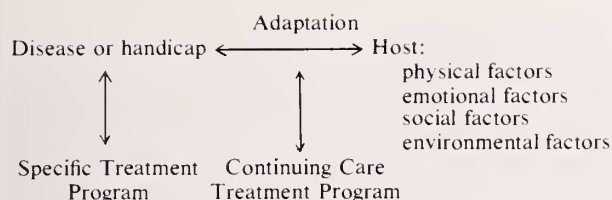
"THE PATIENT SPEAKS"

Please refer to the opening story for the lesson which this patient is trying to teach those who were caring for him.

DISCUSSION

The patient with the stroke syndrome has a number of problems. The approaches to solving these problems provide a textbook for the physician learner. The discussion of this case will focus on only three of the "chapters" in the large volume of information provided. Chapter 1 — The application of the Continuing Care Model. Chapter 2 — The patient with Oral Apraxia as a Primary Speech Disorder. Chapter 3 — The patient as the teacher.

The application of the Continuing Care Model. The term continuing care is not well known in the medical care system. Those who are trying to use it may well be accused of playing a game of semantics. However, the usual connotations of the synonyms rehabilitation, rehabilitation medicine, long-term care, and comprehensive care do not accurately describe the concept. Continuing care not only describes a point or a series of points of time in the continuum of medical care, it also describes the evaluation of a basic physiological, psychological, and at times anatomical characteristic of the human organism — adaptation. This can be diagrammed in the following way:³



Physicians in training are usually exposed to both sides of this model, although the focus is usually sharpest on the disease and the disease specific treatment programs. In the present case, the initial care of the patient, the diagnostic procedures, the treatment programs — all — were examples of perfectly logical and acceptable approaches to this type of patient. However, even in training programs which emphasize the host (patient) and make an attempt to develop meaningful information about the emotional, social and environmental factors rarely is there any specific emphasis on the *adaptation* of the host to the disease(s) and/or its treatment(s).

A logical approach to the evaluation of the adaptation — ability of a patient is a careful description of the patient prior to the present insult or injury. Too long physicians have allowed themselves the delusion that the information contained in the traditional past history, family history, social history, and parts of the review of systems is so unimportant as to not be recorded at all or in a very rote and perfunctory manner. The problem-oriented medical record system promoted by Lawrence Weed, M.D. has placed proper emphasis on the information. In that system, the information is documented first in the patient's record in a section called "The Patient Profile."⁴ Here it is not important to just record the fact that the patient had diabetes mellitus since 1967, but also how the patient reacted to his illness, and to its treatment. Here also, one records as clear a functional picture of the patient prior to the current problem as is possible. What was his normal day like? What are his habits? — his likes? — his dislikes? All of these likes and dislikes will be operative again as he adapts to the stresses of the new disease or condition. The success (or failure) of his adaptation — ability to the new condition will determine the success or failure of the disease — specific treatment program.

THE PATIENT WITH ORAL APRAXIA AS A PRIMARY SPEECH DISORDER

The patient described in this paper was referred to the Aphasia Section of the F.T. Hill Center for Communication Disorders (a department of the Mid-Maine Medical Center) on 12/27/74. However, prior to describing the communication deficits of this patient and his subsequent improvement, it seems pertinent to discuss the types of communication problems Cerebral Vascular Accident patients may develop.

As this patient suffered a stroke to the left hemisphere of the brain, there was good reason to con-

sider the possibility of some form of language and/or speech disorder. Benson and Geschwind in 1971 estimated that 40% of Cerebral Vascular Accidents would produce some disorder of language.⁵ Although the language center is not always found in the left hemisphere, it is currently believed that only a very small segment of the population has a right hemisphere dominance for language, regardless of handedness. Thus, in the vast majority of stroke victims, damage to the left hemisphere causes some impairment in communication skill. Although a Cerebral Vascular Accident is the most common cause of neurologically related language and speech disorders, other causes such as trauma, tumor, infection, or degenerative diseases are possible.

This patient with a Cerebral Vascular Accident like many others could have had three distinctly different disorders of language and speech, or, combinations thereof — Aphasia, Dysarthria or Oral Apraxia. The language impairment caused by the damage to cerebral tissue is commonly referred to as Aphasia. The patient may have difficulty understanding the spoken or written word, and may not be able to adequately express language through speaking or writing. Deficits may be so mild as to go undetected or so severe that the individual is mute. The various types of Aphasia are as multiple as the names given to them. We speak of Alexia, Agraphia, Anomia, Acaculia to name only a few, or we describe language function in terms of specific "can do" and "can't do" behaviors.⁶ The more neurologically oriented speech pathologists describe clusters of symptoms in relation to the location of the lesion — the anterior damage being described as a Broca's Aphasia, while posterior damage is termed Wernicke's Aphasia.

The second possible disorder which is a disorder of the speech mechanism is Dysarthria. It may be caused by lesions to other areas of the brain and is not limited to damage to the left hemisphere. Dysarthria has been described as a weakness, paralysis, or incoordination of the muscles involved in speech production. Thus, the patient's voice production, resonance, and articulation may be affected.

The third disorder will be referred to here as Oral Apraxia. DeRenzi, Pucuro, and Vignolo define Oral Apraxia as the "inability to perform voluntary movements with the muscles of the larynx, pharynx, tongue, lips, and cheeks, although automatic movements of the same muscles are preserved."⁷ For instance, the patient may not be able to voluntarily protrude his tongue, but may do so automatically when a tongue depressor is placed in front of him. Likewise, blowing cannot be accomplished until a lit match is introduced and he automatically will blow it out. He may automatically produce a word accurately through swearing, yet when asked to repeat the word volitionally he may struggle with various incorrect oral postures, produce a number of incorrect phonemes, and still fail

to produce the word accurately. At a less severe level, the patient may utter grammatically complete sentences which vary in intelligibility as he constantly struggles to find the correct placement for his tongue in order to produce the word. Thus, "how are you?" may be produced "how f. . . the . . . sare m. . ah. . . ee you?" It would appear that the patient has lost the volitional neuro-motor pattern of sequencing movements of speech.

Whereas, Aphasia is an impairment at the linguistic level, Oral Apraxia is an impairment at the phonemic level. It has been called Oral-Lingual Apraxia, Phonologic Impairment in Aphasia, Phonemic Paraphasia, Articulatory Dyspraxia, Literal Paraphasia, Perceptual Motor Aphasia, Phonemic Disintegration of Speech, Dysphemia, Oral Motor Apraxia, Verbal Formulation Deficit, Anterior Aphasia to name but a few. Speech Pathologists cannot agree on what to call this disorder, nor can they agree on whether to classify it as a form of Aphasia or as a speech disorder distinctly different from Aphasia. Obviously it cannot fall into the category of Dysarthria, as the Oral Apraxic patient has no paralysis or weakness of the muscles involved in speech. As the true Oral Apraxic patient has no difficulty finding the word he wishes to express or producing a grammatically intact sentence, he should not be categorized as an Aphasic. This writer contends that it is more accurate to place Oral Apraxia in its own category, separate from Aphasia, and separate from Dysarthria. For the purposes of this paper, the disorder will be referred to as Oral Apraxia, a disorder of the neuro-motor pattern of speech movements.

These three disorders Aphasia, Dysarthria, and Oral Apraxia can occur independently or in combinations such as Aphasia with Oral Apraxia, or Aphasia with Dysarthria, etc. Needless to say when occurring in combination, diagnostic evaluation and therapeutic intervention become more complicated.

The patient described in this report who had been transferred to the Rehabilitation Unit from another hospital was first seen for a speech evaluation 24 days after the onset of the Cerebral Vascular Accident. He was subsequently enrolled in a diagnostic, therapeutic program. He has given the standard test batteries utilized by the Aphasia Section of the Hill Center including the Boston Diagnostic Aphasia Examination, the Porch Index of Communicative Abilities, the Minnesota Test for Differential Diagnosis of Aphasia, and various tests of Oral Apraxia. Results indicated that auditory reception was within normal limits with the exception of auditory sequential memory. He could read sentences and respond (non-verbally) but had difficulty of higher levels of functioning, that is, more complex paragraphs. Although he was able to write simple words and sentences, he had difficulty with spelling multi-syllable words and complex sentences. Verbal communication consisted of some vowel

vocalizations, however, he could not spontaneously utter any words, even swear words. He could not protrude his tongue, blow, or imitate tongue or lip movements. All muscles of speech were observed to function normally when eating. Thus, Dysarthria was ruled out. Because of the severity of Oral Apraxia, it was not until after many weeks of therapy that it could be determined if Aphasia was present in oral communication. It was not. The patient showed no difficulty remembering the names of specific words, nor difficulty producing grammatically correct sentences. His verbal communication deficit was one of finding the motor pattern to produce speech sounds — Oral Apraxia. Thus, the initial diagnosis was of a severe Oral Apraxia with some Aphasia, mild Alexia (reading disturbance) and moderate Agraphia (writing disturbance).

The fact that this patient remained in the hospital for 15 weeks was a crucial factor in his rapid speech improvement. On an inpatient basis, it was possible to provide a fairly intensive therapy program — two one-half hour sessions per day, five days a week. The reason that early intensive therapy is vital to the severely Oral Apraxic patient, is that frequently if left on his own he will make such a strong volitional effort to speak that the automatic mechanism does not have a chance to develop to the extent that it would in therapy. In most instances in a person's life, the harder the person tries the more likely he is to succeed — not so for the Oral Apraxic patient. The harder he tries the more volitional his attempts at speaking become and the less the likelihood of success. Early therapy capitalizes on automatic abilities and expands them into usable speech.

From the outset, this patient revealed a strong motivation to obtain the maximum from therapy. If the schedule of the speech pathologist had allowed it, he would have navigated himself from his room to the therapy room four or five times a day. If the hospital escort service was late in bringing him to therapy, he would non-verbally let them know that he was losing valuable time. In the event that the speech pathologist had to be away, she too was reminded by the patient that this was costing him a therapy session.

The patient received over 125 inpatient therapy sessions and 33 outpatient sessions before therapy was terminated due to travel distance and the approaching winter. The majority of the time spent in these sessions was on improving verbal output. Most of the assistance given to improve reading and writing skills was through materials given to be completed on the patient's own initiative during non-therapy "free-time." At the time of this writing (approximately one year after he was stricken) his reading skills are within normal limits and his writing skill, although slow in production, are obviously adequate.

As the severely, impaired Oral Apraxic patient improves, perhaps the greatest problem for him to accept is the "consistency of his speech inconsis-

tency." He may be able to produce the word "door" correctly one moment while the next he says "foor" — "t. . .oor" or "koor", agonizingly aware that his mouth hasn't found the correct position. Sounds may be omitted or substituted. There will be more difficulty with less frequently used words and multi-syllable words. Because of his groping for correct articulatory postures and self-correction, his prosody (melody and rhythm of speech) will be altered and sound deviant. He will often agonize over not being able to say "bed" by himself when he can say it perfectly when the speech pathologist says "you sleep in a"

These are the speech problems that this patient now faces. He can talk in grammatically correct sentences, unless he omits because of a particular difficulty with a specific word. He may substitute "mad" for "aggravate" because it is easier to say. He will not be happy with this circumlocation as "mad" was not the word he truly wanted to use. His speech may be difficult to understand at times, but he will try again to make the word more precise. However, he is now able to communicate verbally. In ten months he has improved dramatically from total mutism to functional verbal communication. He is still in the process of recovering speech and language and undoubtedly will continue to show improvement for an additional 12-14 months.

In the case of this patient as well as other speech and language impaired stroke patients, early therapeutic intervention providing structure, stimulation, and preventing depression were vital factors in his recovery. Equally as important, however, was this patient's own contribution — his determination to recover. Objectively with the aid of diagnostic tools such as the PICA (Porch Index of Communicative Ability) and subjectively through the speech pathologist's own experience with hundreds of cases, it is possible to predict expected levels of achievement. It is the patient himself, however, through self-motivation and determination to improve who enables the speech pathologist to assist him in obtaining and achieving beyond these expected goals.

THE PATIENT AS THE TEACHER

One can add very little to the material contained in the initial paragraph of this article as far as documentation of this principle is concerned. As we contemplate the mechanism of action of corticosteroids on the brain suffering from an acute insult, or as we perform a myriad of sophisticated and expensive radionuclide and electronic tests to pinpoint the location and type of pathology, let us not forget the fact that the patient may be having a problem learning how to tear-off the toilet paper when the roll has diminished to one-third of its normal size. Often, it is the little things which count.

SUMMARY

A case report from continuing care (rehabilitation medicine) is presented. The practical day-to-day problems facing a patient with a stroke syndrome including hemiparesis, and Oral Apraxia as told in the patient's own words are contrasted by the more traditional methods of medical case reporting. Concepts and approaches to evaluation and treatment of the speech disorder of this patient are described. The article emphasizes the importance of a major component of continuing care — that is — treatment based on evaluation of the patient and his adaptation to his disease and/or handicap.

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Reminder to M.M.A. Members

CONTINUING MEDICAL EDUCATION ACTIVITY REPORT

The bylaws of the Maine Medical Association were amended in June of 1973 as follows: Chapter I, Section 11, — "Each member of the Maine Medical Association shall be required to report his activities in continuing medical education every year according to a format provided by the Committee on Continuing Medical Education."

Only active, dues-paying members are required to report this year.

Please fill in your activity report promptly and return to the M.M.A. office, P.O. Box 250, Brunswick, Maine 04011.

Acute Renal Failure

Treatment With Hemodialysis and Parenteral Hyperalimentation at Mid-Maine Medical Center 1973-1975

JOSEPH J. HIEBEL, M.D., F.A.C.P.* and ROSEMARY CAPORALE, R.N.**

Analysis of 14 patients with acute renal failure treated from 1973 through 1975 is reported. This represents our total experience with acute renal failure since our last report in the *Journal of the Maine Medical Association* in February 1973. For the purpose of this report, acute renal failure is defined as a sudden change in urine output associated with rising BUN and Creatinine, reaching levels creating serious difficulties with overall management. None of the patients who are on chronic dialysis programs are included in this report. Patients included were managed by their own physicians in a general hospital until the time the physician felt dialysis was necessary. No patient in the series has required chronic dialysis. The majority of these patients suffered from other medical conditions which were considered to be precipitating causes of their acute renal insufficiency. Unless otherwise specified, hyperalimentation was used in all cases. Results are summarized in Table 1.

TABLE 1

AGE	SEX	DIAGNOSIS	COMMENTS
71	F	Gram Negative Sepsis with Shock and Acute Renal Failure. Cerebral thrombosis. Acute Myocardial Infarction.	Admitted with hemiplegia and previous history of renal stone. Pyelonephritis and Angina Pectoris. High temp associated with Hypotension. Progressive Azotemia, oliguria, and coma developed while in hospital. Three blood cultures were positive for Klebsiella. Klebsiella also was isolated from urine. Following institution of Hemodialysis, I.V. Ancef® and I.V. fluids, coma cleared but hemiplegia persisted. However, the pt. sustained an acute anterior myocardial infarction and expired of cardiogenic shock. Post Mortem: Not granted.
45	M	Septic Shock. Cholelithiasis. Cholecholelithiasis. Biliary Fistula. Bronchopneumonia.	Admitted with severe pain in back with fever and chills. Developed jaundice, obstructive type, and underwent cholecystectomy and common duct exploration. In the postoperative period, he developed draining Biliary fistula and bronchopneumonia. Hypotension and oliguria developed; no response to I.V. Furosemide and increased fluids. Massive doses of Penicillin G, I.V. Hyperalimentation, and dialysis was carried out. After 6 dialysis treatments, renal function improved; pt. has now returned to normal life.
61	M	Cardiogenic Shock. Acute Myocardial Infarction.	Admitted to CCU with massive anterior myocardial infarction, hypotension, pulmonary edema, and progressive oliguria and azotemia. No previous history of renal or cardiac disease. After 26 hemodialysis treatments, renal function improved to point where no subsequent dialysis has been necessary in past 18 mos. Cardiac condition controlled with Lanoxin® alone.
73	M	Renal Failure Secondary to Cholesterol Emboli from Abdominal Aneurysm. Pulmonary Emphysema. Congestive Heart Failure. ASHD.	Admitted for Chronic Obstructive Lung Disease. Progressive rise in BUN and Creatinine developed. Pt. was started on dialysis. Despite treatment, he entered into refractory cardiopulmonary failure and expired. Post Mortem: Done.
70	M	Postoperative Hypotension. Whipples Procedure for Ca Ampulla of Vater. No Metastases. Acute Myocardial Infarction.	Admitted with obstructive jaundice. On exploration, Ca Ampulla of Vater was identified and Whipples Procedure was carried out. Despite adequate fluids and Lasix®, progressive oliguria and azotemia developed. Postoperatively the jaundice cleared. The azotemia was controlled but the patient sustained his third acute myocardial infarction and expired from irreversible cardiogenic shock. No metastases were identified at surgery. Post Mortem: Refused.
28	F	Eclampsia. Acute Post Partem Renal Failure.	Developed seizures post partem in a pregnancy complicated by edema and hypertension. Post partem severe oliguria and anuria developed with rising BUN and Creatinine. After 4 treatments, polyuria followed and renal function is now normal. No Hyperalimentation was done.
62	M	Cardiogenic Shock. Acute Myocardial Infarction. Gout.	Gouty patient with acute myocardial infarction developed hypotension and progressive oliguria, azotemia and cardiac decompensation. Hemodialysis was instituted — promptly clearing the cardiac decompensation. After 10 treatments, renal function returned to the pre-infarction levels. He has been on his own doing well for the past 12 mos. with BUN's in the 50's.

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TABLE I

AGE	SEX	DIAGNOSIS	COMMENTS
65	M	Shock. Myocardial Infarction. Pulmonary edema. ASHD.	Entered with longstanding history of congestive heart failure, angina pectoris and myocardial infarction. This was complicated by embolus to the right lower extremity requiring embolectomy. Following surgery, patient developed progressive oliguria and azotemia and congestive heart failure. Despite dialysis, he expired of refractory cardiac failure. Post Mortem: Yes.
65	M	Pre-renal Azotemia Secondary to Paralytic Ileus. Hepatic failure. Pancreatitis. Cholelithiasis. Chronic cholecystitis and Cholelithiasis.	Admitted with obstructive jaundice. Explored, found to have cholelithiasis with secondary pancreatitis and common duct obstruction. During post-op period had paralytic ileus. Prolonged hyperalimentation was necessary. Finally, he was dialyzed 1 time due to rising BUN and fear of progressive renal failure. Improved, thought to have had pre-renal azotemia.
73	M	Acute Tubular Necrosis Multiple Rib Fractures. Atelectasis. Bronchopneumonia. Hepatic Lacerations with Hemorrhage. Coronary Arteriosclerosis.	Admitted after being run over by a tractor. Multiple bilateral rib fractures with atelectasis and G.I. bleeding. Pt. had hypotension, progressive oliguria and azotemia. Hemodialysis was carried out 2 times before irreversible shock with cardio-pulmonary failure developed. Post Mortem: Done.
59	M	Myeloma Kidney. Multiple Myeloma. Bronchopneumonia.	Admitted with severe pain in back associated with pathological fractures L ₂ L ₃ due to Multiple Myeloma. Urine Electrophoresis showed Lambda Light Chains. Pt. developed Bronchopneumonia and expired after 1 dialysis. No Hyperalimentation done. Post Mortem: Done.
56	M	Cholesterol Emboli to Renal Arteries. Post Aneurysm Surgery. Diabetes. ASHD.	Admitted for aortic bypass for abdominal aneurysm. Had had carotid endarterectomy 4 weeks before and myocardial infarction 2 years earlier. In post-op period, no hypotension developed but progressive oliguria and anuria developed. After 9 Hemodialysis treatments, pt. stabilized and has now been off dialysis for 1 year and stable.
30	F	Acute Tubular Necrosis. Shock. G.I. Bleeding Due to Diffuse Hemorrhagic Gastritis. Diabetic Ketoacidosis. Bronchopneumonia. Anoxic Brain Syndrome.	Juvenile diabetic admitted with Diabetic Keto Acidosis and Hematemesis and melena. Vomited, aspirated, and had cardiac arrest with prolonged C.P.R. Bilateral bronchopneumonia and hypotension developed complicated by progressive oliguria and azotemia. Pt. was comatose after C.P.R. and never regained consciousness. Despite MA1 and hemodialysis 2 times, Flat EEG developed and Harvard Criteria of Death were met. No Hyperalimentation done.
54	M	Acute Hemorrhagic Pyelonephritis. Ca Pancreas with Hepatic and Adrenal Metastases. Bilateral Bronchopneumonia. Cirrhosis of the liver.	Admitted with progressive abdominal pain and distention and a previous history of alcoholism. The diagnosis of pancreatitis with secondary obstructive jaundice and liver failure was entertained. However, pt. did not respond. A CEA Titer of 22 raised the question of Carcinoma of pancreas. Exploratory surgery was done and Ca pancreas with hepatic metastases was identified and progressive renal failure ensued. The pt. finally expired after 5 treatments. Post Mortem: Done.

SUMMARY

Clinical and postmortem findings are listed in each case in the table above. It should be noted that there was no increased morbidity or mortality associated with the institution of dialysis. In every instance, patients who were postoperative were given regional dialysis. Those patients unable to take normal alimentation were treated with hyperalimentation through subclavian veins. In each case where the patient expired, the cause of death was not the withdrawal of dialysis but progression of other medical conditions beyond the reach of hemodialysis. As expected, those patients with the fewest medical complications did best. Those with the most advanced diseases expired earliest. It should be noticed that two patients with shock complicated by myocardial infarction required the longest

period of dialysis, 26 times in one case, and 10 times in the other. Both of the post infarction patients made good recoveries and no longer require hemodialysis.

CONCLUSION

The occurrence of acute renal failure in the face of multiple medical and surgical problems represents a serious limiting factor in the proper management of the other underlying diseases. Early hemodialysis makes possible proper intravenous fluid and hyperalimentation treatments to prevent metabolic deterioration. Time can be gained that allows the other conditions to be brought under control, and in some instances, results in a significant reduction of the mortality rate and morbidity.

Dr. Hiebel, 179 Main Street, Waterville, Maine 04901.

Management of Multiple Trauma*

JOHN F. REYNOLDS, M.D.,** ALBERT J. PEPE, M.D.,†

H. RICHARD HORNBERGER, M.D.‡ and JOSE RODRIGUEZ, M.D.‡‡

Dr. Reynolds:

There have been questions in our minds concerning the way we should handle multiple trauma, especially as to whether we should develop a team concept. This works well in large teaching hospitals but I am not sure that we can handle it quite the same way here. Several of us have discussed this but nothing definite has evolved even though we work together with one person in charge. Surgeons and others concerned must agree on certain basic procedures and treatment — these we will discuss today. I have asked Dr. Richard Hornberger to say a few words about chest trauma, Dr. Albert Pepe to speak about orthopedics, Dr. Jose Rodriguez to discuss craniocerebral injuries and I will discuss abdominal trauma.

In 1973, injuries were the fourth leading cause of death. There was an increase in vehicular accidents, although in the past year these are down because of changes in speed limits. Suicides are up and homicides are up. More powerful weapons and more confrontations between militant groups and law enforcement agencies make the subject an increasingly complex and frequent one.

The three main types of abdominal trauma are stab wounds, shotgun wounds and blunt injuries. Seventy percent of such patients reaching the hospital alive will have extra abdominal associated injuries about equally divided between craniocerebral, and ribs and pulmonary damage. Initial care means the maintenance of function of the vital organs. There must be an adequate airway maintained as is appropriate via means varying from an Ambu bag to a cuffed endotracheal tube. Adequate circulation must be maintained; two large bore IV lines should be placed (preferably to one side of the patient) to monitor CVP and administer fluids. A Foley catheter should be inserted early, possibly a Levine tube may be needed and a chest tube is frequently required for chest injuries. During this phase of treatment, the patient should be in the emergency room. The patient should not be transported to x-ray, to the laboratory or even to the ICU

until basic treatment has been given and conditions are somewhat stabilized.

After the initial measures have been taken, the order of definitive treatment must be established. Cardiac tamponade or arrest takes precedence over all other injuries. Abdominal wounds take precedence over peripheral injuries except for control of hemorrhage and splinting of fractures. One of the most important things I have learned over the past several years concerning abdominal trauma is how to do effective paracentesis for evidence of blood or other extravasated fluid. Many surgeons still use four quadrant taps or intracaths or other equipment but in my experience a peritoneal dialysis catheter is the most effective instrument. The catheter is inserted in the midline of the abdomen under local anesthesia (the bladder having been previously drained). After placement of the catheter in adults, a liter of lactated Ringer's solution is run into the abdominal cavity and allowed to run back by gravity. In children, about 500 cc.'s of Ringer's lactated solution can be used. Pink staining of the return fluid indicates a need for laparotomy. You can do hematologic determinations, check amylase and perform other tests on the recovered fluid but basically if pink stained fluid comes back there is an adequate indication for laparotomy.

Insofar as stab wounds are concerned, there are two major philosophies of treatment. Some suture a catheter into the wound, inject Hypaque under pressure and take AP and lateral films. This is a good procedure if it is positive, but negative results of course mean very little. I think more and more of those concerned with this subject are observing patients carefully and repeatedly over twenty-four to forty-eight hours. If no peritoneal signs develop, there is no indication for laparotomy. However, if there is doubt about the need for exploration, then the proper thing to do is explore.

In gunshot wounds, laparotomy is always indicated. The patient should be explored as soon as possible and the precise spots of injuries identified and treated as is appropriate.

The most common abdominal injuries are those of blunt trauma. Most often these injuries involve the spleen or liver. Time does not permit detailed remarks about the various organs, so I will omit comment except to remark about liver lacerations and injuries. More and more surgeons are doing hepatic artery ligations rather than major lobe resections of the liver. If the hepatic artery is ligated, it should be done close to the source of the hepatic artery.

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Effective diagnosis and management of the patient with multiple trauma depends on a regular sequence of procedure. These are:

First and most important — repeated careful examination of the patient.

Abdominal paracentesis.

Careful evaluation of vital signs.

CBC, hematocrit, and amylase. Arterial blood gases are often required.

X-rays of the chest and abdomen — intravenous pyelogram is often indicated.

Arteriography and isotope scans if needed.

Dr. Pepe:

I will discuss some of the important aspects of orthopaedic injuries as they relate to the multiple trauma patient. More specifically, what should one think of in the patient who has multiple fractures and soft tissue injuries that are associated with abdominal, chest or head trauma?

An immediate consideration is that of blood loss which can be significant in various fractures and may confuse the clinical picture in evaluating a patient in shock from abdominal blood loss. A fractured femur commonly involves loss of 2 units of blood when it is of the closed type and 3 or 4 units if it is an open fracture. Pelvic injuries with fractures of the pelvic ring commonly cause the loss of many units of blood. It has been shown that in fractures involving the pelvic ring, the blood loss is proportional to the number of fractures.

A second consideration is that of the initial evaluation of an extremity injury with regard to the neurologic and circulatory status. It is extremely important to document the status of the extremity at the beginning because if this is not documented, confusion arises later as to what may have produced a deficit after treatment has begun. This is not only important in establishing a plan of treatment but also from the medical-legal point of view. This may be difficult in the patient with head injury or with a patient in shock but the examination must be made and recorded.

In general, most extremity injuries are considered secondary when a treatment plan is formulated in the patient with abdominal or chest problems. However, there are certain injuries that should be given as much priority as other organ systems. Every effort should be made to obtain an early reduction of a dislocation especially in a joint such as the hip because the long-term result may very well depend on early treatment. It is well known that the longer the hip is dislocated, the greater the chance for problems with an avascular necrosis of the femoral head at a later date. On most occasions, the reduction can be performed in the emergency room if the patient is unconscious or at the time of anesthesia being administered for treatment of other organ system injuries. Of course, vascular injuries demand immediate treatment and the appropriate

approach to an associated fracture in the area is made at the same time. Open fractures should be considered for relatively early treatment and debridement. Usually this can be performed at the time of surgery for other purposes.

I should also mention the question of internal fixation of various types of fractures. In general, it is considered inappropriate to perform internal fixation in compound fractures unless specific circumstances dictate otherwise. This type of approach should definitely be considered in the head injury patient who is likely to be unconscious and uncooperative and whose agitation may be difficult to control. In this type of patient, traction often is a poor choice for immobilization whereas internal fixation is very useful.

It is also important to consider the problem of fat embolus. This is a significant problem in the multiple trauma patient, especially in those with long bone injuries. The most important consideration is, of course, recognition. In the patient without head trauma, a change in mentation should prod one to begin looking for evidence of fat embolus. Arterial blood gases are generally a reliable means of establishing the diagnosis if the patient has not had concomitant chest trauma. The characteristic changes on chest x-ray with the multiple infiltrates are also helpful. Most of the other signs are quite variable including the appearance of petechiae, depression of the platelet count, and the findings of fat particles in the urine. The filtration test to demonstrate fat globules greater than 8 microns in diameter correlates very well with the clinical onset of fat embolism syndrome but is quite complicated to perform in the usual hospital setting.

The treatment of fat embolism should involve respiratory support to the extent dictated by changes in the arterial oxygen. This is usually best provided in an Intensive Care Unit setting. I personally prefer the use of steroids rather than other advocated methods which include the use of heparin, concentrated glucose, and alcohol.

In summary, much of the treatment plan for orthopaedic injuries in the multiple injured patient is basically the same as that for a patient with isolated extremity trauma. However, it may prove useful to consider the above comments and recommendations when one is dealing with a broken head, broken ribs and broken bones.

Dr. Hornberger:

I will try to make this short and pertinent in terms of our local situation. Any casualty who has sustained trauma to the chest should be considered seriously injured until proved otherwise. This is another way of saying, don't let anyone die of a potential problem. Most hospitals in Maine do not have a house staff. Consequently, the care of seriously injured is up to physicians who are busy taking care of many other patients, often in more than

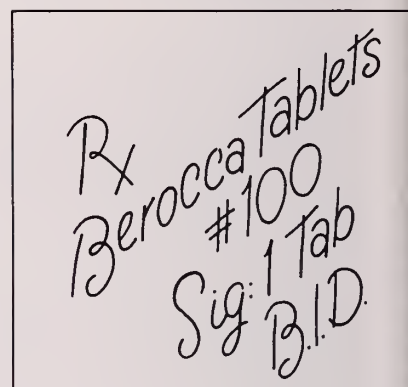
one hospital. Therefore, when one treats someone with any kind of significant chest injury, I think that one should overplay it. I have seen a variety of chest injuries in the eighteen years I have been in Waterville. The more injuries I see the more I think that overtreatment is the right road. I remember vividly seeing a man who really didn't seem to have much of an injury — he had a little pneumothorax and a few broken ribs. His physician, however, was concerned and I was asked to see him. I told the physician that I thought the patient needed a tracheostomy and to be on a respirator. This was about fifteen years ago when respirators weren't as commonly used as at present. I left thinking that I had made a reasonable recommendation but that it was up to the physician concerned to do the tracheostomy and set up the respirator. I didn't really think that this was an emergency. If I had then had the benefit of my last ten years or so of experience, I would have stayed and seen to it that the patient was taken care of immediately. I didn't do that at that time and the man died some twelve hours later. Although I have seen people with chest injuries get well with far less treatment than we use routinely nowadays, the point I am making is that if there is anything wrong with the patient — particularly at night — do a tracheostomy, put a tube in the chest if there is a hint of a pneumo or hemothorax and either put the patient on a respirator or have a respirator immediately available along with someone who knows how to use it.

To further illustrate my thesis, let me tell you about another patient whose injury occurred while I was away. The patient, a farmer in his early seventies, had been run over by a tractor. There were multiple fractures of the ribs, a fractured scapula and separation of the sternoclavicular joint. He also had a hemothorax. Dr. Marshall did a tracheostomy, put a tube in the chest and put him on a respirator. The patient proceeded to get well. This was because the formula was followed. I inherited the patient when I got back from vacation. In the next four weeks, I wrote about three orders on his chart. The patient doesn't remember the physician who originally took care of him because he was so sick during that period and so he thinks I saved him. One of the arguments people have in this and other similar cases is how horrible the chest x-ray looks and it is suggested that there should be a more dependent drainage tube. On a recent visit to Toronto to get further educated in this sort of thing, I heard that clotted hemothorax should almost always be operated. I personally think this is rarely necessary. As in this patient, most of the time chest film and pulmonary function returns to normal without surgical intervention. One thing I haven't mentioned so far and that I have talked about much in the past is stabilization of the flail chest. Until a few years ago, I would have said that the patient with

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multiple fractured ribs should need something to stabilize his chest. This, however, is not necessary today because of the use of the respirator — although I heard a discussion recently in which one or two people still said they used stabilization.

Another important fact is that a major injury to the chest can lead to pulmonary problems. We have previously discussed fat emboli. The only thing that I can add is that in addition to using heparin and steroids, one should think of multiple fat emboli as being about in the same league as pulmonary edema; and that peak end expiratory pressure (PEEP) is an important adjunct in treatment.

I'll discuss a second case that relates to pulmonary aspects of chest injury. One of the things we have heard much about in recent years is shock lung, pump lung, Da Nang lung or whatever you want to call it. I recently heard someone say that this has only been discovered in the last ten years. In Korea twenty years ago, we called it traumatic wet lung. I think probably this next patient is a fair example of it. This is a patient who jumped off a bridge. I don't think anyone was there to rate the jump but I think he probably wouldn't have gotten more than a 2.5 because he landed sort of all over. He had a small pneumothorax on the right side. A tube was put in place. He had a tracheostomy. He was in shock on admission and needed fluid. If a rib makes a hole in a lung, the hole is the size of the rib; but if the patient receives too much Ringer's lactate, pretty soon the lesion becomes three or four times the size of the original hole because of the excess fluid flowing into the injured area. Therefore, it pays us to be circumspect about how much fluid we give patients, and to think in terms of albumin and whole blood instead of Ringer's lactate. To get back to the patient, his left or uninvolved lung developed a whiteout after his shock had been treated. I suspect the patient received excessive fluids because the lung cleared reasonably rapidly with treatment with corticosteroids and diuretics.

I don't completely understand the business of shock lung and postoperative respiratory insufficiency. Some people have suggested that it is often the result of so called "heroic cycle" — "the emergency room to operating room to intensive care unit syndrome" with all kinds of things going on and perhaps someone losing track of what is going on. I talked to a friend in another part of the country recently who was asked to see a surgical patient who had a bilateral whiteout of both lungs and who was in extreme respiratory distress. The patient had a subclavian line and an IV in an arm vein. Various medications were given through both lines but the orders on the subclavian line were "T.K.O." — to keep open. That used to mean technical knock-out and I think it often still does mean technical knockout. The intake and output for this patient was recorded for the subclavian line but no one knew how much the patient was getting in the other

IV. Striking out from the ward my friend went to the business office and said he wanted to know how many bottles of intravenous fluid had been charged to the patient. He came back with two typewritten pages, single spaced. The patient had been getting about 9,000 cc's of fluid a day which accounted for the whiteout of his lungs. We have to be increasingly aware of this kind of trouble be it after trauma or after surgery.

Dr. Rodriguez:

In listening to Dr. Hornberger and Dr. Pepe, it becomes clear to me that we all are using the same treatment for different problems. The orthopaedic and chest surgeons are using corticosteroids to prevent fat embolism and the neurosurgeon is using them to prevent cerebral edema. Most of the time, the multiple trauma patient is first seen by an emergency room physician, a general practitioner, or a general surgeon. For that reason, I believe a neurosurgeon should stress some points which should be observed in patients who also have a head injury.

The first point I would make is not to give morphine to patients with head injury. After the patient has received morphine, it is very difficult to evaluate the neurological status because morphine constricts the pupils, may change the state of alertness or response and also may increase respiratory difficulties. These changes make neurological evaluation very difficult. Progressive intracranial pathology can be missed.

The second point concerns the amount and speed of the intravenous fluids given the patient. I have noticed many times on entering the Emergency Room that two IV's are running wide open even when the patient is not in shock. For that reason, I would suggest that the physician who first sees this type of patient carefully regulate intravenous fluids because excessive fluid may increase cerebral or pulmonary edema. Most multiple injury patients, with head injuries as the main factor, are not going to be in shock. Should a patient be in shock, I prefer to use plasma expanders or blood when available instead of the usual saline or electrolyte solutions. I have never seen head injury produce shock by itself with the exception of patients in the terminal stage just preceding respiratory and cardiocirculatory arrest. Most patients with head injuries have a normal blood pressure. If the intracranial pressure starts to rise to a dangerous level, the blood pressure rises in an attempt to compensate and improve the cerebral circulation. This elevation of the blood pressure plus slowing of the pulse rate, labored respirations and sometimes inequality to the pupils are warning signs of rapidly rising intracranial pressure and the immediate need for neurosurgical intervention.

Now what should be done in a head injury patient until a neurosurgeon is available? I believe that the first thing to do is to secure a good airway by putting

in an endotracheal tube or doing a tracheostomy if indicated. If the patient's condition permits, elevate the head about thirty degrees in an attempt to decrease the intracranial venous pressure. Decreases in intracranial pressure have been demonstrated very dramatically by measuring the intracranial pressure as the head is being elevated from a horizontal position to thirty to forty degrees. I also always use intravenous corticosteroids as soon as possible in order to prevent the development of cerebral edema. The usual dose is 8 milligrams of dexamethasone bolus plus another 8 milligrams in each 1,000 cc. of fluid (given at a rate of about 80 cc.'s per hour).

Another point I would like to stress is that most head injuries can be managed during the first few hours by a general surgeon or an emergency room physician following the outline above.

The only injuries that require the immediate attention of a neurosurgeon are compound depressed fracture of the skull with evidence of brain injury manifested by brain substance being apparent in the wound or by severe bleeding in the area. Epidural hematoma also requires early attention. These usually produce symptoms within a few hours. The typical situation is a patient, conscious or unconscious for a short period of time after the accident, who develops symptoms of restlessness, progres-

sive loss of consciousness, and usually dilated pupils and weakness or paralysis of one side. In this situation, surgery is indicated as an extreme emergency. When an intracranial clot is suspected, arteriographic studies are indicated.

In regard to the other type of neurological injuries, I would only say that in spinal cord injuries it is very important to move the patient with care, because a sudden change in the axis of the spine may cause a severe injury. Another point that is important in a suspected spinal cord injury is to do a good but rapid neurological evaluation for motor or sensory changes. A lateral x-ray at the appropriate level of the spine should be done at once when there is a question of injury. Management of the peripheral nerve injuries should wait until the other more pressing problems have been solved and the patient's condition has stabilized. Finally, in the case of the patient who arrives at the emergency room completely paralyzed with a flaccid paralysis that occurs immediately after the accident, the outcome is usually very poor and there is very little that can be done surgically to change this outcome.

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Dr. Hornberger, 325 Kennedy Memorial Drive, Waterville, Maine 04901.

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Pyogenic Vertebral Osteomyelitis

DAVID R. GINDER, M.D.*

Pyogenic infections of the vertebral bodies and their intervening disk spaces are usually described as rare or uncommon. However, in a 3-year period in one unit (170 beds) of the Mid-Maine Medical Center, 2 of a total of 23 admissions for osteomyelitis were for pyogenic vertebral osteomyelitis. The patients are reported here to re-emphasize the puzzling presentations of pyogenic vertebral osteomyelitis,^{1,2} to point up the use of bone scan as an aid in diagnosis, and to stress the advantage of newer treatment.

PATIENT SUMMARIES

Patient 1 — A 56-year-old laborer entered the hospital complaining of right-sided chest pain of 3 weeks' duration. The patient attributed the pain to an accident in which a heavy metal object hit him in the chest anteriorly. He fell away, landing on his chest posteriorly. The patient also noted low-grade fever, night sweats, and a 25-pound weight loss. The pain in the right chest was poorly localized; many times it seemed to be located in the right upper abdomen. Chest film taken just prior to admission revealed right pleural effusion; the intervertebral spaces were normal. Physical examination revealed a febrile (100.5° F.) obese man in no acute distress except when he coughed or tried to move his chest. No vertebral tenderness was elicited. The only positive finding was dullness, decreased breath sounds, and rales in the right lower lobe and the right middle lobe. Significant laboratory findings: E.S.R. — 51 mm/hr. Pleural fluid contained 2.4 grams of protein, 2600 red cells and 2000 white cells with 70% polys/mm. Routine, fungal, and tuberculosis cultures revealed no growth. Investigation was directed to the possibility of carcinoma of the lung, thromboembolic disease, pulmonary tuberculosis and subdiaphragmatic disease. Studies for these possibilities were negative except for a 23 ml. reaction to Int. PPD. At this point, 3 weeks after admission, a lateral chest film revealed decreased interspace between T7 and T8 that had not been present the initial weeks of hospitalization. Bone scan done at this same time revealed abnormal uptake at T7 and T8 vertebrae. Percutaneous biopsy was attempted without success. At open operation, penicillinase resistant *Staphylococcus aureus* was isolated from disk tissue. The patient was treated with intravenous medications for 6 weeks. Treatment was complicated by a nafcillin drug eruption and a cephalothin urticarial reaction. The final treatment was accomplished with vancomycin. Other complications of the prolonged immobilization and hospitalization included thromboembolic disease with pulmonary emboli. Thirteen months after treatment the patient was entirely healthy and preparing to go back to work.

Comment — Poor localization of the pain caused initial difficulty in the diagnosis. Contrary to most patients with pyogenic vertebral osteomyelitis, no loss of intervertebral space was apparent on admission. Also on admission, and for some period thereafter, there was no localized vertebral tenderness. Loss of interspace and abnormal bone scan were noted the same day. Once the loss of interspace occurred the only problem was establishing the nature of the infection. The patient was treated with the older type regime consisting of debridement, rigid immobilization, and intravenous antibiotics. While this treatment was effective, it is apparent that the consequences of long rigid immobilization — thromboembolic disease and general weakness — did contribute to prolonged loss of work.

Patient 2 — A 47-year-old office manager while at work, noted the sudden onset of severe pain in the thoracic area. The pain became worse and radiated laterally on both sides and occasionally down to the buttocks. The pain lasted seconds to minutes. Any movement of the back, or even a deep breath, made the pain intolerable. Although the patient has spondyloepiphyseal dysplasia, it never had caused restriction of activity. Physical examination revealed a well developed and nourished man in intense pain. The only positive finding was that the patient could not thoroughly be examined because the slightest movement of almost any part of the body caused intense pain. The temperature rose rapidly to 104° F. During the first two days while the temperature ranged between 101 and 104° F., major efforts were directed to controlling pain and to determine whether pain arose in the heart, lungs, or elsewhere. After 6 blood cultures were taken, the patient was started on a cephalosporin antibiotic. The temperature fell to normal in 36 hours and the pain gradually came under control. By the third hospital day with the pain under reasonable control, it became clear that the pain was localized in the lower dorsal back and radiated around both costal margins and up and down lateral to the spine. Physical examination at this time failed to show any localizing signs. There was no tenderness over any of the vertebra. On the same day, 6 of 6 blood cultures were positive for penicillin sensitive *Staphylococcus aureus*. X-ray films of the dorsolumbar spine and laminograms revealed no significant abnormality. However, bone scan utilizing Technetium-99 revealed abnormal uptake at T10. When the antibiotic susceptibility of the *Staphylococcus aureus* was known, the patient was started on 24 million units penicillin-G intravenously daily. After 6 weeks of parenteral treatment, the patient was discharged home taking penicillin-V 500 mg. 4 times a day for another 6 weeks. The patient was allowed bathroom privileges after the first week of hospitalization, and was walking with the aid of a Jewitt extension brace four weeks after hospitalization. He had returned to full-time work four months after the onset of the illness in apparent perfect health. In convalescence, roentgen signs of spontaneous arthrodexis were noted.

Comment — The sudden onset of the pain was unusual in pyogenic vertebral osteomyelitis. The pain was unusually severe and required large amounts of narcotics. Only when the pain was reasonably well controlled was it possible to determine that the pain originated somewhere in the thoracic back. At the same time, the positive blood cultures, in the absence of signs and symptoms pointing to endocarditis, suggested the possibility of pyogenic vertebral osteomyelitis even though there was no localized pain over the vertebra. Plain films and laminograms were difficult to interpret because of spondyloepiphyseal dysplasia. The bone scan, however, revealed marked density at the T8 level. The clinical course and the lab data made a strong case for pyogenic vertebral osteomyelitis. The positive blood cultures demonstrated the etiology. Treatment consisted of simple bed rest and intravenous antibiotics. Contrary to the long convalescence of the first patient, this patient returned to full-time work 4 months after the onset of his illness.

DISCUSSION

Pathogenesis and Etiology — Although the first changes by conventional x-ray are seen in the intervertebral space, there is good reason to believe that pyogenic vertebral osteomyelitis begins in the vertebral body in adults and older children. This is so, because beyond early childhood the intervertebral disks have no vascular supply.³ *Staphylococcus*

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aureus and gram negative organisms are the most common causes of pyogenic vertebral osteomyelitis. The usual mechanism of infection of the vertebra is by bacteremia carried to the body of the vertebra via the nutrient artery. Quite often, however, the bacteremia is remote, so that in about 50% of cases, no history of antecedent infection can be obtained.⁴ It is popular to implicate Batson's venous communication system from prostate and pelvis to lumbar vertebra in explaining pyogenic vertebral osteomyelitis following pelvis and prostatic surgery or spesis. Though this mode of pathogenesis is possible, but unproved, it is much more likely that bacteremia from prostate and pelvis sources causes lumbar pyogenic vertebral osteomyelitis.⁵

Diagnosis — The basic tools for diagnosis of pyogenic vertebral osteomyelitis are sequential conventional x-rays and laminograms of the vertebra. Because of the relatively large bone mass in vertebra, it takes weeks to months to demonstrate clear-cut loss of bone even with laminograms. Usually the first roentgen sign is loss of intervertebral space caused by spread of infection to the intervertebral disk. This is an important sign; it virtually stamps the process as one of infection. Metastatic tumor does not destroy intervertebral space. The place of bone scan in the diagnosis is not established, but it seems quite possible that a positive bone scan can be demonstrated before conventional films and laminograms reveal abnormalities. When the bone scan is positive in the clinical setting of pyogenic vertebral osteomyelitis, it helps one to cone down on the correct diagnosis. On the other hand, in the setting of cancer metastatic to the vertebra (possibly complicated by gram negative bacteremia), if the bone scan is positive and x-rays are negative, it will be necessary to differentiate infection from metastatic tumor.

Specific diagnosis of the etiology of pyogenic vertebral osteomyelitis is required for intelligent treatment. If the diagnosis cannot be established by positive blood cultures, closed or open biopsy with appropriate stains and cultures are required. Whether blood cultures are positive depends on the organisms involved, the state of the infection, prior antibiotic treatment, etc. Overall, perhaps 20-30% of patients with pyogenic vertebral osteomyelitis have positive blood cultures. Success in percutaneous biopsy is highest in lumbar vertebra for technical reasons; open biopsy is almost always positive when specimens are properly stained and cultured.

Signs and Symptoms — Common complaints are dull constant pain of long duration, usually localized over the involved vertebra. The most common signs are rigidity of the involved vertebral column, adjacent paraspinal muscle spasm and exquisite pain or pressure over the spine of the infected vertebra. Malaise and low-grade fever are frequent. These are rather simple signs and symptoms, but patients often have pain without vertebral rigidity and muscle spasm for such a long time they become lost

in the vast legion of patients with back pain. In other patients, pain such as that which occurred in the two reported patients, confuses the picture. The first patient had pleuritic pain but he also had a poorly localized anterior and posterior chest and abdominal pain. The second patient had bilateral pain running laterally and vertically from the affected vertebra — sometimes suggesting referred pain and sometimes consistent with root pain. Neurologic signs and symptoms also occur when the infection spreads to cause extradural abscess and meningitis. Rarely the infection can spread beyond the vertebra to cause pleural effusion, empyema, retropharyngeal abscess, mediastinitis, and subdiaphragmatic infection.

The crux of the matter is to think of the diagnosis when back pain is accompanied by localized vertebral pain, low-grade fever and an increased ESR. Bone scan should be obtained in patients with normal conventional x-rays before ordering laminograms because it seems likely that they become positive a significantly long time before laminograms. In the patients reported, both bone scans were positive. In the second patient, bone scan was positive before conventional films or laminograms revealed clear evidence of disease.

Treatment — Prior to the advent of antibiotics, pyogenic vertebral osteomyelitis was treated with debridement and rigid immobilization for long periods of time. Antibiotics were added to the older regime without critical evaluation of whether debridement and long rigid immobilization was still needed.³ However, increasingly over the past 15 years, patients have been treated with long-term antibiotics and simple immobilization in bed.² Results have been good, but physicians have been slow to accept these regimes because such treatment regularly fails in osteomyelitis of the long bones. Whatever the gross and microscopic difference between osteomyelitis in long bones and vertebrae, a major difference is that in long bones sequestrum almost always forms. On the contrary, in pyogenic vertebral osteomyelitis, sequestration is minimal or absent. This is a significant difference because sequestrum acts as a foreign body and prevents response of osteomyelitis to antibiotics alone. In uncomplicated pyogenic vertebral osteomyelitis, current concepts of treatment require large amounts of antibiotics given parenterally for about 6 weeks, followed by 6 weeks of oral medications. It is important to note that although the presence of spontaneous arthrodesis is a strong indication of successful treatment, many patients have recovered fully without roentgenologic evidence of fusion.

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300 Consecutive Gastroscope Examinations

Analysis of Findings

LUCIEN F. VEILLEUX, M.D., F.A.C.S.*

With the advent of fiberoptic endoscopes, esophago-gastro-duodenoscopy has become increasingly valuable. However, few reports have been published analyzing the significant lesions of consecutive endoscope procedures.^{1,2} The findings, of course, may well vary with the patient population and physician selection. This paper analyzes my personal experience with three hundred consecutive examinations utilizing the Olympus GIF Type-D endoscope. All abnormalities were photographed. All patients had an upper GI examination with barium within a few days of gastroscopy. Most of the roentgen examinations preceded gastroscopy.

INDICATIONS

1. Unexplained upper abdominal and chest pain.
2. Upper GI bleeding.
3. Equivocal x-ray findings.

CONTRAINDICATIONS

1. Moribund patient.

TECHNIQUE

1. General anesthesia.

This is a controversial approach in that most endoscopists use local anesthesia. I have adopted general anesthesia for the purpose of providing patient comfort. It also supplies an element of physician comfort. Many patients, who had previously been gastroscoped under local anesthesia, expressed their appreciation of general anesthesia. None have refused repeated examinations.

I have experienced occasional difficulty in entering the esophagus. This has been minimized by preliminary dilatation of the proximal esophagus with a #36 blunt-tipped mercury weighted bougie. The additional maneuver of elevating the lower jaw has also been helpful.

On rare occasions the endotracheal tube was momentarily removed to allow passage of the gastroscope.

2. Position.

Patients were examined in the supine position.

COMPLICATIONS

1. Retropharyngeal hematoma.

ANALYSIS — 300 CONSECUTIVE GASTROSCOPY EXAMINATIONS

# Of Diagnoses	Diagnosis By Endoscopy	Endoscopy Diagnosis Confirmed By GI Series
<i>Esophagus:</i>		
28	Esophagitis	0
22	Ulcer	0
11	Stricture	11
16	Hiatus hernia	16
3	Carcinoma	2
4	Varices	1
<i>Stomach:</i>		
6	Hemorrhagic gastritis	0
15	Erosions	0
30	Ulcers, benign	18
2	Marginal ulcers	0
1	Giant rugal folds	1
5	Polyps	0
2	Leiomyoma	2
7	Carcinoma	6
2	Obstruction of gastro-duodenostomy 2° hypertrophy	2
<i>Duodenum:</i>		
10	Duodenitis	0
5	Erosions	0
6	Pyloric canal ulcer	4
16	Duodenal ulcer	9

This was the only instance in which the gastroscope could not be passed into the esophagus. The hematoma resolved without complications.

ILLUSTRATIVE CASES

C. W. — 66-year-old mentally retarded female was admitted with postprandial right upper quadrant pain radiating into back. Cholecystogram: Normal. GI Series: Hiatus hernia. Endoscopy: Large esophageal ulcer. Multiple biopsies negative for carcinoma.

T. G. — 48-year-old female with constant periumbilical pain for 2 months. Pain not related to meals. GI Series: Duodenal diverticulum. Endoscopy: Multiple 3-4 cm. antral ulcers and two deep duodenal ulcers.

S. B. — 45-year-old female admitted with black stools and hemoglobin of 10 gms. Occasional eructation and epigastric pressure. Similar episode 2 years previously. Barium enema: Normal. GI Series: Normal. Endoscopy: Two benign antral ulcers.

H. W. — 70-year-old female with 3 months of epigastric pain after meals associated with a 10-lb. weight loss. Patient had subtotal gastrectomy with Billroth II anastomosis 10 years previously. GI Series: Possible carcinoma of stomach. Endoscopy: Marginal ulcer.

DISCUSSION

In three hundred endoscopy examinations, there were 179 diagnoses in 154 patients. Upper gastrointestinal series revealed only 72 abnormalities in

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the same group of patients. As expected, endoscopy was particularly helpful in examination of the esophagus for all lesions except hiatus hernia. Data not included in this analysis suggests that endoscopy misses about 50% of hiatus hernia diagnosed by upper gastrointestinal examination with barium.

As expected, upper GI series did not detect superficial gastric erosions, gastritis, small gastric polyps and marginal ulcers. Naturally, duodenal erosions and duodenitis were also missed by the barium examination.

Endoscopic examination of the stomach and

duodenum also revealed a considerable number of benign ulcers that were not visualized by GI series. On the other hand, benign ulcers, visualized by upper GI series were missed by endoscopy, particularly in the duodenum.

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Subacute Sclerosing Panencephalitis

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Subacute Sclerosing Panencephalitis (SSPE) is a rare degenerative disease of the central nervous system which primarily affects children of school age and which usually terminates fatally often within one year of its onset. When this entity was originally described by Dawson in 1933, the finding of intranuclear inclusion bodies led him to postulate a viral etiology for the disease which he at the time termed "subacute inclusion body encephalitis." Subsequent descriptions of diseases termed "nodular panencephalitis" by Pette and Doring and "subacute sclerosing leukoencephalitis" by Von Bogaert are felt to be examples of what is now termed SSPE.¹

The viral etiology postulated by Dawson was eventually proved. Connolly, et al² and others³ demonstrated the presence of high titers of measles antibody in serum and cerebrospinal fluid of affected children and also, by immunofluorescence, the presence of measles antigen in cerebral cortex. In 1969, the isolation of a measles virus from a brain biopsy of a patient with SSPE was accomplished.⁴ Additional studies have since shown that SSPE virus isolates are antigenically identical to wild measles viruses strains although for certain serologic studies they are more closely related to the laboratory adapted vaccine strains.⁵

The clinical picture of SSPE is rather stereotyped although exceptional cases have been reported. The course has been divided into three or four stages.^{6,7} The patient initially demonstrates an insidious deterioration of intellectual function along with mental changes characterized by emotional lability and gradual deterioration of speech. Brief, sudden myoclonic jerks involving head, limbs and trunk then appear which occur rhythmically at intervals rang-

ing from 5-20 seconds. The electroencephalogram (EEG) reveals characteristic periodic bursts of high voltage slow waves which can be seen to occur in association with each myoclonic jerk. Initially of low amplitude, the myoclonus becomes more severe so that a patient who is trying to walk might be thrown to the floor by its occurrence. As the course progresses, a host of other neurologic findings develop including gross incoordination, tremors, choreoathetotic postures, and spasticity. The child remains awake but has little or no speech. Finally coma supervenes accompanied by signs of hypothalamic dysfunction including hyperthermia, profuse diaphoresis, and pulse and blood pressure disturbances. Most patients have succumbed at this stage although some pass on to a form of chronic vegetative state in which they may remain for months or years. However, there have also been documented cases of SSPE not progressing to such a severe degree of compromised neurological function that have shown spontaneous remission.^{8,9}

SSPE is more common in males by a factor of 2.5-4 males for each female affected^{1,5} and the great majority of reported cases are in children from rural areas. The estimated frequency of the disease is one per million population, indicating that approximately one case per year on the average will be seen in Maine. The case presented here is that of a patient seen and diagnosed last year at the Mid-Maine Medical Center.

CASE REPORT

P.M., a 10-year-old boy, was admitted to the Mid-Maine Medical Center in October 1974. He had been in good health until August of that year when his parents became aware of a number of behavioral changes. They noted particularly at the dinner table recurrent, brief, little dropping, or nodding, movements of his head. During these episodes he seemed momentarily "out of contact" with his surroundings. As time passed, they noted that his gait was becoming unsteady and that his hands demonstrated shakiness when used in fine, skilled movements. The patient was

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Fig. 1-(a), EEG (11/1/74): Background rhythms at 5-7 cps with some 3-4 cps activity present. Two examples of the high voltage slow wave complexes are seen approximately 8 seconds apart. Note in each channel the similarity of waveform of the two bursts.

seen by a physician who ordered a number of tests including an electroencephalogram (EEG). The EEG was read as showing diffuse slowing and bursts of high voltage 2 cycles per second (cps) delta activity. It was interpreted as indicating probable serious cortical dysfunction. The child was placed on Dilantin® 50mg. t.i.d.

When the patient returned to school in September, it then became apparent that intellectual function had deteriorated. Reading and arithmetic were performed with increasing difficulty. Multiplication tables and simple problem solving that he should have been able to do were performed less and less well. His speech became noticeably slurred and then became marked by word-finding difficulty. Throughout this time, the intermittent, nodding head movements were present.

Past medical history was noteworthy in that the patient was diagnosed as having measles at age 6 months. He also had both mumps and chickenpox at age 3 years. Immunizations were complete except that measles vaccine was never given because of the prior history of the disease.

On admission, the patient was a well-developed and well-nourished appearing 10-year-old boy in no acute distress. Observing him one noted single, brief, jerking movements occurring rhythmically at approximately 10 second intervals affecting the head, trunk and/or limbs. They appeared either as little nodding movements of the head or as slight lapses of postural stability. The general physical examination was within normal limits. On neurological examination, he appeared as an alert and responsive boy who was able to give a reasonably good description of his difficulties. His speech was occasionally slurred and he did have evident interruptions suggestive of either word-finding difficulty or lapses in his train of thought. He could not readily name all the months of the year in order, but after some effort, he named 11 of them. Tests of reading and arithmetic indicated he was functioning 4-5 years below his age-appropriate level. Cranial nerve examination was normal except for the left eye which demonstrated an acuity of 20/200 (The visual problem had been present since early childhood.). Muscle strength and tone were normal. The gait was mildly wide-based and ataxic and was periodically interrupted by the brief lapses noted above. It made the patient lurch slightly in one direction or another as he walked. Coordination testing revealed mild-to-moderate ataxia on finger-nose-finger testing, and there was moderate decomposition of rapid skilled and rapid alternating movements. Deep tendon reflexes were 2+ and symmetrical in the upper and lower extremities. Babinski responses were absent bilaterally. The sensory examination revealed intact primary and cortical sensory function. Routine laboratory studies revealed: Hgb. 11.5,

Hct. 34.3, and WBC 4400 with a normal differential. The following were also normal: urinalysis, SMA-12, serum protein electrophoresis, skull x-ray, and brain scan. The EEG (Fig. 1a) demonstrated moderate and diffuse slowing of the background rhythm (5-7 cps) superimposed on which were bursts of bilaterally synchronous high voltage slow waves appearing periodically at intervals of 8-9 seconds. At the time of the EEG recording, the nodding movements of the head and/or jerking movements of the limbs were noted to occur in association with the periodic slow wave bursts. A lumbar puncture revealed an opening pressure of 110mm C.S.F. with crystal clear fluid containing 3 RBC's and 0 WBC's. The protein was 22mg% and the glucose was 51mg%. A.C.S.F. protein electrophoresis yielded a markedly abnormal globulin/albumin ratio of 0.9444 (normal less than 0.222). Serological studies for measles virus complement fixating antibody were drawn. The serum titer was 1:128; the CSF titer was 1:32. A diagnosis of SSPE was made in this patient, and after thorough discussion of the prognosis with the parents, the patient was discharged on the 6th hospital day.

The patient returned to the hospital two days after discharge because of vomiting and dehydration. He was acutely ill-appearing, was able to follow commands, but did not speak. The general physical examination revealed signs of dehydration but was otherwise unremarkable. The neurological examination was noteworthy in that the deep tendon reflexes were brisker than the week before and exhibited unsustained ankle clonus and positive Babinski responses bilaterally. The patient was given IV fluids, and over a period of three days brought back to a state of normal hydration. From this point on, it became apparent that he was undergoing significant neurological deterioration. He was emotionally labile, demonstrated diminished verbal ability and exhibited extrapyramidal ("cogwheel") rigidity. The EEG (Figure 1b) exhibited some 5-7 cps rhythms, but now contained a good deal of 2-4 cps activity not so prominently seen in the previous tracing. In addition, the high voltage waves making up the periodic complexes were of lower amplitude. The interval between complexes had not changed. The periodic myoclonic jerks seen previously were now seen against a background of almost continuous, very low amplitude, multifocal myoclonic jerks. The patient was started on nasogastric tube feedings. As time passed, the myoclonus became less severe and the patient began to assume a posture of generalized flexion (fetal posture). At the end of the second week in the hospital, the patient was begun on Isoprinosine, an experimental oral anti-viral agent (obtained from Dr. Richard Mattson, Department of Neurology, Yale University School of Medicine), which is undergoing investigation as a treatment for SSPE. No immediate effects, either

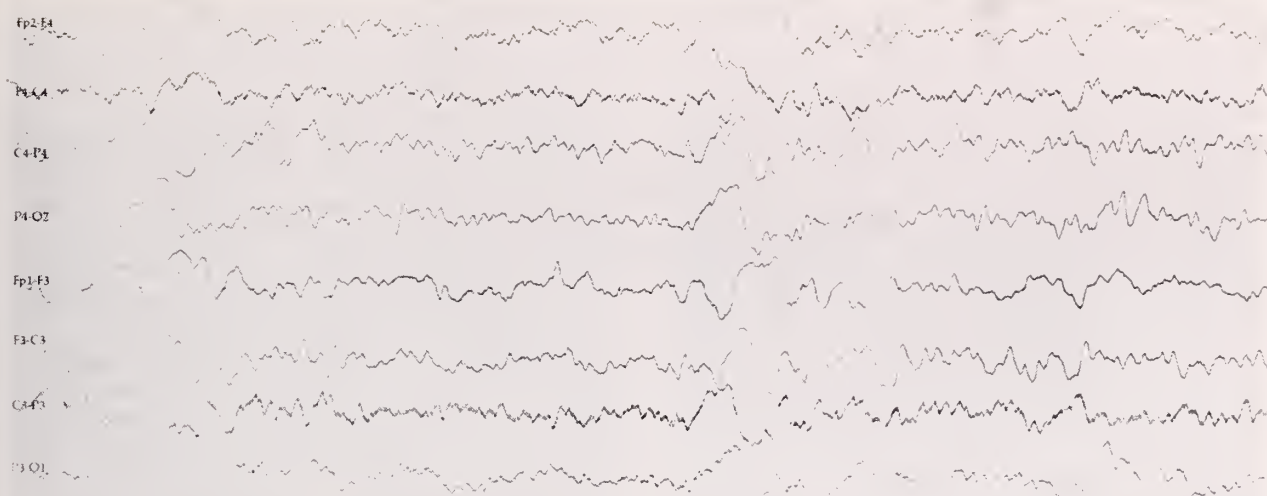


Fig. 1-(b), EEG (11/12/74): Background rhythms at 5-7 cps with more slow activity than seen in previous tracing. Note that the periodic bursts are of lower amplitude than previously and are beginning to "blend" into the background.

beneficial or detrimental, were noted after the drug therapy was begun. Shortly thereafter, because of the hardship imposed on the family to travel the considerable distance to Waterville, he was transferred to a hospital in his home town. There his condition continued to deteriorate apparently unaffected by the Isoprinoline. Terminally he developed signs of hypothalamic dysfunction with high fever and unstable blood pressure. He died 3½ months after his illness first became apparent.

DISCUSSION

The clinical presentation and the laboratory data in this patient leave no doubt as to the diagnosis of SSPE. Unfortunately, pathological confirmation could not be obtained as permission for autopsy was refused. Nevertheless, the progressive impairment of neurological function, associated with the characteristic, periodic myoclonus conforms well with published descriptions and with previous cases of SSPE seen by the author. In addition, positive findings were obtained in all three significant laboratory tests: 1) elevated CSF gamma globulin, 2) elevated serum and CSF measles antibody titers, and 3) abnormal EEG demonstrating periodic complexes.

The EEG received attention early in the history of SSPE because the periodic events were such outstanding and recognizable phenomena that some observers felt them to be pathognomonic of the disease. Subsequent investigation tempered this overly dogmatic point of view when it was noted that periodic complexes might also be seen in Creutzfeldt-Jacob disease (subacute spongiform encephalopathy), progressive myoclonus epilepsy (Lafora body disease, Unverricht-Lundborg disease), cerebral lipidosis, anoxic encephalopathy, and herpes simplex encephalitis. However, if one considers the case history, the age and clinical picture of the patient (as well as the morphology and inter-burst interval of the complexes in the EEG); it is in fact relatively easy to distinguish SSPE from

the aforementioned diseases.¹⁰ In SSPE, the patient is usually a school age child although cases ranging from ages 2-32 have been reported.¹¹ With the occurrence of myoclonus one sees high voltage slow wave complexes appearing in a quasi-regular ("periodic") fashion most commonly at 5-15 second intervals and synchronously from both hemispheres. For an individual patient, the complexes seen in any given EEG will be nearly constant in form and will occur at a nearly regular interval.^{10,12} There have been reports of a shortening of the interval between bursts as the disease progresses.¹² When the first EEG taken on the patient (September 10, 1974; in another city) was re-read, it appeared that the slow wave bursts mentioned in the original report were in fact recurring in a periodic fashion. The interval varied from 11-14 seconds; thus, there was a decrease in the inter-burst interval over the succeeding weeks to the 8-9 seconds recorded in the EEG's at the Mid-Maine Medical Center. As the disease progresses, the complexes become less well defined and disappear while the background rhythms themselves become slower and more disorganized. This can be seen in the examples from our patient (Figure 1). The timing of these changes in relation to the clinical condition of the patient and the pathological state of the brain is somewhat variable, but follows an over-all pattern. The trend obtained from correlative neuropathological studies is for the periodic complexes to be most clearly present when the disease is clinically not far advanced and the cerebral cortex, still relatively well preserved.¹⁰ From the neurophysiological aspect, this is of interest as it implies that functioning cortex is necessary for the occurrence of the complexes. The trigger mechanism for the burst is felt to be in the brain-stem reticular formation wherein also lies control over the sleep-awake cycle. In SSPE, the myoclonic jerks disappear dur-

ing sleep while the complexes seen on the EEG continue to be recorded. In both the waking and sleep states, the complexes appear to have a rhythm of their own and are very difficult to disturb with auditory, visual, or tactile stimuli.¹² For those few patients showing remission of the disease, the EEG similarly exhibits improvement.^{8,13}

CSF gamma globulin is characteristically increased in SSPE and often represents the highest levels seen in any disease states. The serum gamma globulin is not abnormal. This fact together with available experimental evidence indicates that the excess immunoglobulins are in fact produced within the central nervous system. Other diseases which may manifest increased CSF gamma globulins include neurosyphilis, multiple sclerosis, or any systemic disease (cirrhosis, myxedema, collagen disease, etc.) causing an increased serum gamma globulin. As noted above, the clinical picture will be most important in addition to other tests in distinguishing an SSPE patient from one with another disease who also has elevated CSF globulin level.

The discovery of the relationship between measles virus antibody and SSPE led to the recognition by electron microscopy, of paramyxovirus nucleocapsids in brain tissue and eventually to the isolation of a measles virus from brain cell cultures using cocultivation techniques. One study of large numbers of SSPE patients (59) and controls (83) has shown that the complement fixation (CF) test for measles antibody is the most valuable in that the presence of measles CF antibody in the CSF suggests SSPE, while its absence precludes the diagnosis, particularly if antibody determinations are repeatedly negative.¹⁵

The association of measles viruses and SSPE is referred to as a slow virus infection patterned after the descriptions of chronic viral infections in sheep known as scrapie, visna, etc. The precise pathogenesis of the disease is unknown, but is probably dependent on certain immunological mechanisms. In the brain cell, the SSPE virus is in a latent phase related to its inability to mature into an infective virus particle by budding at the cell membrane. This latent stage accounts for the difficulty originally encountered in attempting to isolate an infective agent from SSPE brain specimens by traditional techniques.^{5,14} The nature of the slow virus infection implies that the agent is present for some time prior to the onset of clinical symptoms. Epidemiological studies demonstrate an over-representation of early measles infections (under 2 years of age) among a large group of SSPE patients.¹⁶ The age of occurrence of natural measles and subsequently of SSPE in these patients suggest a possible "incubation period" for SSPE of 6 to 7 years.^{16,17} One theory proposes that early measles infection (especially under 1 year of age) occurs in the presence of small amounts of remaining maternal antibody thereby preventing a "normal" immunological response on

the part of the host. This allows the virus to establish itself in a unique fashion in which the host makes circulating antibodies but in which cellular immunity is defective, and the virus remains latent in cells for years. It has also been reported that SSPE developed in patients immunized in infancy with live measles vaccine. At the present time, however, there is no evidence that measles vaccine has increased the risk over-all of SSPE. It might be noted in this context that the patient reported here apparently had measles at age 6 months and then developed SSPE 9 years later.

In broader perspective, the discovery of the relation of measles to SSPE points to the possibility that other neurological diseases are the result of "slow" virus infections. Kuru, a degenerative disease of the Fore people in New Guinea was the first such disease shown to be transmissible to animals. Creutzfeldt-Jacob disease, one of the senile dementias, has been transmitted to chimpanzees. In neither of these two latter cases has a specific virus been isolated. Finally, mention should be made of multiple sclerosis for which a viral etiology has long been considered. In the early 1960's, reports of measles antibody in the CSF of multiple sclerosis patients were published. Repeated studies have corroborated this relationship although none of the data has ever been so impressive as that relating measles to SSPE. More recently there have been reports of viral-like particles seen by electron microscopy in acute multiple sclerosis lesions. The possibility is implied that an even more bizarre relationship exists between measles virus and host in multiple sclerosis than it does in SSPE.

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Endometriosis

Treatment With Danazol

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INTRODUCTION

In a recent conference on endometriosis, leading authorities reported that endometriosis is occurring more frequently and at an earlier age than previously described.¹ Others have reported that endometriosis is a far more common problem than previously believed, that 50% of women have it in different degrees of severity. They believe that many women with pelvic complaints labelled psychosomatic are in reality cases of endometriosis.²

There is general agreement that endometriosis can be a serious illness. Two patients treated at Mid-Maine Medical Center confirm the severe character of the advanced stage of endometriosis.

CASE REPORTS

Case 1 — A 36-year-old gravida 0 was admitted to the hospital on 3-9-75 with a complaint of severe lower abdominal pain and a complete bowel obstruction. Surgery performed on 3-13-75 demonstrated massive bilateral endometrial cysts with generalized implants over the entire pelvis and involving the uterus, ovaries, lateral pelvic wall, cul-de-sac, and bowel. A 12 cm. segment of the colon behind the uterus was involved with narrowing of the lumen, induration, and extreme kinking causing a total obstruction of the bowel.

Total hysterectomy, bilateral salpingo-oophorectomy and a colectomy was performed. The patient had an uneventful post-operative course and was discharged on the 10th day following surgery.

Case 2 — A 38-year-old gravida 2, para 2 was admitted to the hospital on 5-18-75 with a history of intractable dysmenorrhea, chronic low back pain, and progressively more severe obstipation accentuated several days prior to, and with her menstrual periods.

At surgery on 5-20-75, a large endometrial cyst of the left ovary, 16-18 cm. in diameter was demonstrated, with generalized endometrial implants over the cul-de-sac, and two lesions involving the sigmoid colon 4-5 cm. in length with transmural involvement causing a partial obstruction.

Hysterectomy with salpingo-oophorectomy was performed with no attempt made to resect the bowel lesions. The patient had a mild ileus for several days following surgery which responded to a conservative regimen. She was discharged on the 11th post-operative day.

DEFINITION AND ETIOLOGY

Endometriosis is a proliferation of endometrium in any site other than the uterine mucosa. This is a 20th century disease. The true beginning of scientific studies on the subject came in 1921 with the observations of John Sampson who described endometriosis as the presence of ectopic tissue which possesses the histological structure and function of uterine mucosa. It also includes abnormal conditions which may result from invasion of organs

and other structures by this tissue and from its relation to menstruation. Though endometriosis is a benign condition, it can invade tissue and disseminate itself or metastasize by hematogenous or lymphatic routes or by implantation. The three theories of the etiology are (1) retrograde menstruation, (2) abnormal differentiation of coelomic epithelium, and (3) dissemination via lymphatics.³

DESCRIPTION OF CONDITION

Whatever the etiology, ectopic endometrium resembles uterine mucosa responding to stimulation of ovarian hormones. The tissue shows cyclic changes characteristic of menstruation. Since there is no outlet for the menstrual discharge, blood and debris collect within the tissue to form a cyst. With each menstrual episode, the collection increases in size but continuous absorption of the fluid elements causes the blood to become inspissated and dark colored (chocolate cysts).

As the cyst grows, its endometrial lining is thinned out and eventually destroyed. Large chocolate cysts as frequently found in the ovary are lined by granulation tissue or by pseudoxanthoma cells rich in hemosiderin and the real nature of the condition is not diagnosed by the pathologist. For this reason, endometriosis is not diagnosed in 50% of the cases.

LOCATIONS OF ENDOMETRIOSIS

Endometriosis can occur anywhere in the body and has been described in tissues of the arm, leg, pleura, diaphragm and kidney. The usual sites are confined to tissues and organs of the abdomen and pelvis below the level of the navel. In order of decreasing frequency, the common locations are ovary, peritoneum of the pouch of Douglas, and outer coat of the uterus. In 1922, Sampson published a long paper on intestinal endometriosis. This initial paper has been followed by numerous reports from other authors over the years.^{4,5,6,7,8}

Symptomatology of endometriosis with involvement of the bowel include severe dysmenorrhea, metromenorrhagia, intermenstrual pain and dyspareunia, diarrhea with menstruation, constipation usually more severe immediately prior to and with the menstrual flow, low back pain and pressure pain in the rectum during menstruation, and a relatively rare symptom, bleeding from the bowel.

DIAGNOSTIC SIGNS AND STUDIES

1. Palpation of nodular irregular induration in the

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cul-de-sac especially palpable through the rectal mucosa. (This is as conclusive as any diagnosis in medicine.)

2. A barium enema may be of value if there is an obstruction.
3. Laparoscopy or laparotomy may be necessary in order to establish a definitive diagnosis.

TREATMENT OF ENDOMETRIOSIS

1. Conservative treatment with estrogens and progestins which has been a long established treatment of this condition. Recently this has been questioned and criticized because it increases the size of the uterus and makes it more hemorrhagic. Hormonal administration also makes the implants soft and friable.
2. A conservative surgical approach for minimal disease includes dissection of the bowel lesions, resection of ovarian cysts, excision of implants in the cul-de-sac, presacral sympathectomy, and uterine suspension. The aim of conservative therapy is to remove as much tissue as necessary and as little as possible.
3. If fertility is not a consideration, hysterectomy and bilateral salpingo-oophorectomy represents the optimum surgical approach to the problem of advanced endometriosis. With more conservative surgery, 30-35% of the patients will require additional surgery within nine years.
4. Treatment of endometriosis with bowel involvement
 - A. With minimal lesions, local excision with total hysterectomy and salpingo-oophorectomy.
 - B. With more extensive involvement of the bowel more radical surgery is indicated. A report by Lamon Gray from the University of Louisville presented the following series of cases with bowel involvement:
 - 50 cases were treated with excision of the bowel lesion without entering the lumen.
 - 14 had resection of the anterior wall of the rectosigmoid or sigmoid colon.
 - 8 had resection of a complete segment of the lower colon from 5-18 cm. in length with end-to-end anastomosis.⁹

USE OF DANAZOL IN THE TREATMENT OF ENDOMETRIOSIS

Danazol 2,3-isoxazol, 17 α -ethinyl testosterone.

Recently several investigators have reported dramatic results with a new drug, Danazol, an antigonadotrophic agent effective in the treatment of endometriosis. Doctors Lauersen and Wildon reported in studies from New York Hospital on a trial of this agent in 32 patients with extensive endometriosis. With a dosage of 800 mg. daily for six

months, 28 or 87.5% of the patients showed marked improvement in both clinical signs and subjective symptoms.

Greenblatt and Bornstein tried Danazol in 48 infertile patients with proven advanced endometriosis. All of these patients had responded unsatisfactorily to prior treatment with conservative surgery and hormone preparations. The overall pregnancy rate of this group on Danazol was 40.6%.¹⁰

In another study by Greenblatt and Bernard, Danazol was given in doses of 800 mg. daily for from 21 to 240 days to 62 patients. Symptomatic improvement occurred in 55% of the cases and 42% conceived within four months after discontinuing therapy.¹¹

Since the initial cause of endometriosis is not affected by treatment with Danazol recurrence is always possible. To date, however, the recurrence rate has been very low in the reports from many investigators.

There are side effects with Danazol, but these appear to be minimal and in no way similar to the serious effects obtained with large doses of estrogens or oral contraceptives. As there is no estrogenic or progestational activity from the drug this has obviated all the bleeding problems encountered with older therapeutic regimens involving those hormones.

The most common side effects reported with patients on Danazol therapy have been the following:

1. Decreasing breast size has occurred in many women on therapy. Because of this effect, Danazol has been used for treatment of women with fibrocystic breast disease with some reports indicating as high as a 60% success rate.
2. Weight gain particularly in teenage girls.
3. Less common side effects reported included night sweats, oiliness of the skin, clitoral hypertrophy, and acne.

Recent investigators have questioned the 800 mg. dosage and favor a 200 mg. daily dose which they believe is adequate and will significantly reduce side effects.

CONCLUSION

Endometriosis is a frequent finding in females and can be a serious condition. Since the symptomatic picture and usual signs presented by endometriosis can be found in varying degrees in almost every case, it is important to consider the condition in each female presenting with pelvic complaints. Two cases have been presented which were complicated by bowel involvement causing intestinal obstruction.

Treatment should be individualized with careful consideration of the optimum regimen for each specific patient. Factors such as the extent of the disease, and the attitude of the patient concerning

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An Unusual Case of Infectious Mononucleosis in a Child

DOROTHY I. EISENGART, M.D.*

The child with fever, malaise, and marked pharyngitis is a frequent visitor to the practicing pediatrician. His rapid response to appropriate antibiotics or ability to readily recover in their absence (or in spite of their use) is often noted.

However, the less commonly observed patient, with lingering and progressively worsening symptoms of acute upper respiratory disease, may present an enigma. Once believed to be an entity restricted to adolescents and young adults, Infectious Mononucleosis (IM) is being confirmed in younger children.^{1,2} Whatever its protean presentation, the diagnosis rests on appropriate clinical signs and hematologic evidence. The latter may render confusing results initially, as in the following case presentation. The relative lymphocytosis, appearance of atypical lymphocytes in the peripheral blood, antibodies to Epstein-Barr (EB) virus and abnormal differential heterophile titer appeared either late or not at all in the clinical course.

CASE REPORT

An 8-year-old white girl was hospitalized at Mid-Maine Medical Center, Seton Unit, with complaints of stomach pains, headache, and fever to 105 F for five days prior to admission. During the three months preceding hospitalization, she had lost 11 pounds. On admission to the hospital, she appeared chronically ill with a temperature of 104 F, regular pulse of 136/min., injected tympanic membranes, injected 3+ tonsils and clear but pale skin. She had many small non-tender lymph nodes palpable in both the anterior and posterior cervical triangles and in both axillae. Cardiac exam revealed a regular sinus rhythm with slightly muffled S1, a widely split loud S2, and a II/VI short systolic ejection murmur best heard at the third left intercostal space, left sternal border. The abdomen was diffusely tender; liver edge was sharp and felt at the right costal margin. The spleen was slightly tender and the tip was felt 4cm below the left costal margin. The remainder of the physical examination was non-contributory.

Initial blood studies revealed a white blood count (WBC) of 1700 with 44 polys, 8 bands, 43 lymphs, 4 monos and 1 eosinophile. Sed rate was 8 mm/hr.; hemoglobin 12.1 gm%, hematocrit 34% and platelets were slightly decreased. For subsequent important hematologic and chemical indices, please refer to Table 1. Initial urinalysis revealed a specific gravity of 1.030, 10 mg% Albumin, 20-30 White Blood Cells/hpf, and 1+ acetone. Subsequent urines were normal only toward the end of hospitalization. Monospot was negative and remained so when retested. Lumbar puncture was completely normal. EKG demonstrated: a.) intraventricular conduction delay, b.) first degree heart block, and c.) non-specific T wave flattening.

Chest x-ray was negative. Bone marrow aspiration performed the day following admission revealed a shift to the left in granulopoiesis with no blast increase, and reticuloendothelial hyperplasia. It was judged to be consistent with an infectious process. Cultures of blood, bone marrow, urine, throat, and

spinal fluid were negative. Initial liver function studies were elevated and rose further during the hospital course (see Table 1). Cold agglutinins, febrile agglutinins, CRP, and ANA were negative. Hepatitis associated antigen was not detected by counter current electrophoresis. Carcinoembryonic antigen (CEA) assay initially was 6.2 ng/ml (normals less than 2.5 ng/ml) consistent with an inflammatory response with disruption of basement membrane. Repeat CEA in 3 weeks was 2.7 ng/ml. For Immunoelectrophoresis values, see Table 2. The findings, including a marked decrease in haptoglobin and increase in alpha 1-antitrypsin were interpreted as consistent with an acute mild inflammatory response.

The clinical course exhibited wide frequent temperature swings throughout the first 2½ weeks of hospitalization. Table 3 depicts the curve during the first hospital week (the second week being almost a duplicate of the first). The patient was supportively treated with antipyretics and a cooling blanket. Antibiotics including Ampicillin were instituted together with IV therapy. The medication had no positive effect on the clinical course and was discontinued following an appropriate trial and corroboration of negative cultures.

During daily physical examinations, no rash was observed. The spleen size correlated well with the peripheral WBC. That is, the spleen was larger when the peripheral WBC was low, and smaller with an increased peripheral WBC.

By hospital day 16, the peripheral WBC was only 2800, liver and spleen were enlarged, yet the patient clinically was much improved. On day 19, titers to Epstein-Barr virus were determined to be significantly elevated. By day 26, total WBC was 4200, the patient was afebrile, less anorectic, and was discharged on iron and low fat, high protein, high carbohydrate diet. Low hemoglobin and hematocrit were no doubt affected by the numerous venipunctures performed for laboratory studies.

Post-hospitalization blood work is also noted in Table 1.

COMMENT

It became increasingly evident that this patient indeed had Infectious Mononucleosis, eventually confirmed by positive EB viral titer and appearance of atypical lymphocytes in the peripheral blood.³ The child met Evans modified criteria for the diagnosis of Mononucleosis: a.) clinical manifestations b.) lymphocytosis, with atypical lymphocytes present, c.) a positive differential heterophile, or a positive EB virus titer, and d.) evidence of hepatic dysfunction.⁴

The heterophile test is reported as a presumptive heterophile titer, a guinea pig kidney titer, and beef RBC titer. Heterophile antibodies produced during IM are not absorbed by guinea pig kidney cells, but are by beef RBC. Most individuals have some heterophile antibodies.⁵ Therefore a titer of 1:56 is accepted as the lower significant limit in the presumptive heterophile. Titers vary depending on the stage of the disease. In this patient, the differential titers were reversed from the situation expected in IM.⁶ However, as the EB virus is implicated as the etiologic agent of IM,^{7,8,9} the positive viral titers

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TABLE 1

SUMMARY OF LABORATORY FINDINGS								
Lab. Value	Hospital Day						Post-Hospital Month	
	1	3	5	11	17	25	1	10
WBC cu mm	1700	2900	2900	3900	4700	4900	5600	7000
Hemoglobin gm%	12.2	12.3	11.3	11.3	10.2	10.7	12.5	12.8
Polys %	44	40	42	27	24	12	15	30
Bands %	8	5	14	11	2	2		4
Lymphs %	43	50	41	59	65	84	84	59
Monos %	4	5		3	5		1	4
Platelets	sl.	sl.		adeq.				
Sed Rate mm/hr	8			20				
Atypical Lymphs %	0	25	30	15	10	8		4
Juveniles %			1		1			2
Monospot	Neg.			Neg.				
Heterophile (unabsorbed)	1:448					1:448		
Heterophile: after guinea pig	1:14					1:56		
Heterophile: after beef cell	1:112					1:224		
EB virus antibodies					+++			
LDH (normal 46-124 u)	930			1:200				
SGOT (normal 2-45 u)	179			1275		681	627	
Alk. Phosphatase (normal 9-35 u)	42.2			657		150	240	
Triglycerides (normal 50-150 mg/dl)	197			221		205	75	
CPK (normal 0-52 u)	48.7			149		300	111	
Blood glucose (normal 70-115 mg/dl)	94.8			12.7		60.9	86.8	
				98.9		98.9	75.5	

in this patient would confirm the diagnosis. It has been noted that in childhood, infection with EB virus (a member of the Herpes group) is frequent. In a series of patients, Tamir et al report a rise of EB virus antibody titers 1-2 months following the onset of disease. EB virus antibodies were absent in patients tested within 2 weeks of the onset of their illness.¹⁰

The usual substantial increase in IgG, and IgM¹¹ in IM was lacking in this patient. The markedly low level of haptoglobin is puzzling. Haptoglobin, (Hp) an alpha-a-glycoprotein binds with hemoglobin to form a stable complex. The complex is cleared from the circulation by cells of the Reticulo Endothelial system. When hemoglobin (Hg) is liberated into plasma in excess of the synthetic ability of the liver for haptoglobin, depletion of haptoglobin results.¹² This is noted in acute and chronic hemolytic states. This patient did not demonstrate frank hemolysis. Perhaps splenic trapping of the Hp-Hg complex, and or deficient haptoglobin production due to hepatic compromise contributed to the low level.

One interesting feature displayed by this child was the absence of a rash following Ampicillin administration. It has been previously observed that children with IM are more likely to develop a rash when given Ampicillin. The pathogenesis is suggested to be linked to interaction between EB virus and Ampicillin; the mechanism is unknown.¹³

The overwhelming initial clinical presentation of this case reflected multi-system involvement; unstable temperature presumably of hypothalamic origin; renal, with abnormalities seen in early urinalysis; clinical cardiac and EKG findings suggesting mild myocarditis with minor disturbance of the conduction pathways; lymph node and spleen in-

TABLE 2

IMMUNOELECTROPHORESIS		
FRACTION	RESULTS	NORMAL
Total Protein	7.4	6.0-8.0 gm/DL
Albumin	3.4	3.5-4.5 gm/DL
Alpha-1-Antitrypsin	560	200-400 mg/DL
Haptoglobin	<20	30-180 mg/DL
Alpha-2-Macroglobulin	440	150-420 mg/DL
Transferrin	410	200-400 mg/DL
Complement, C ₃	210	100-200 mg/DL
IgG	1040	660-1760 mg/DL
IgA	148	60-320 mg/DL
IgM	196	50-200 mg/DL

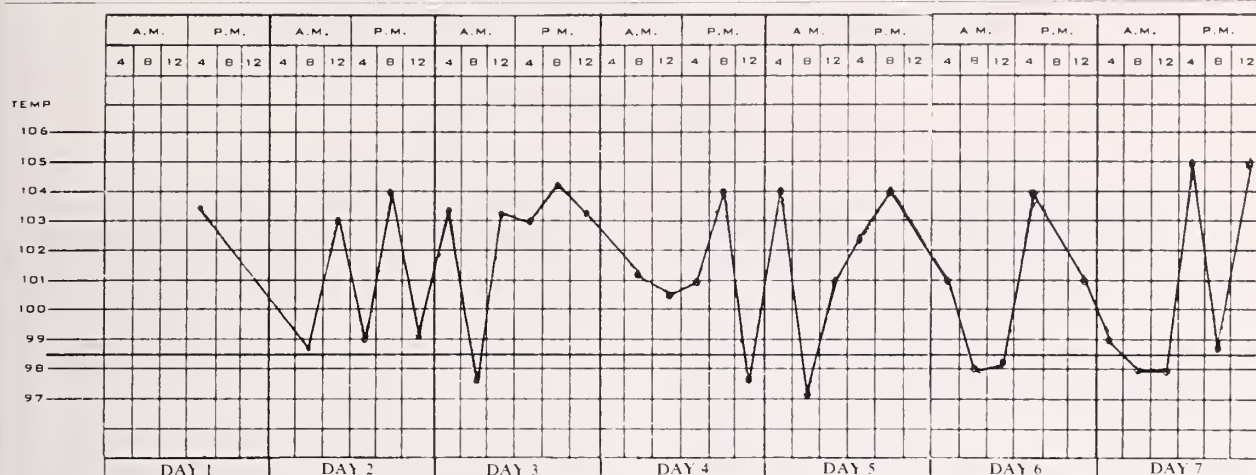
volvement; and finally hepatic derangement, leading to anicteric hepatitis. In spite of the perplexing onset and early course, and marked toxicity of this patient, severity in each affected system was limited and recovery thus far (1 year post onset of known illness) has been complete. The prognosis in this and in most other individuals with IM, despite the duration and degree of morbidity, is excellent.

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TABLE 3

TEMPERATURE CURVE DURING THE FIRST WEEK OF HOSPITALIZATION (DEGREES F°)



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PYOGENIC VERTEBRAL OSTEOMYELITIS — Continued from Page 41

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SUBACUTE SCLEROSING PANENCEPHALITIS — Continued from Page 46

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Spring Meeting of the M.M.A. House of Delegates

Saturday, April 3, 1976

Eastern Maine Medical Center, Bangor, Maine

12:30 P.M. — Registration; 1:00 P.M. — Lunch; 2:00 P.M. — Meeting

10:00 A.M. — Meeting of the Executive Committee

Report on a Government Sponsored Pediatric Dental Program

ROBERT E. DETRICH, D.D.S.*

HISTORY AND DESCRIPTION OF CLINIC

The Thayer Hospital dental program for children of low income families began as a result of a study done by the Northern Kennebec Community Action Council. This study included economic data for Waterville and Somerset County, and confirmed the large percentage of low income families and the significant level of transient employment based on seasonal work. Previous studies have shown that Maine children have the worst dental health of any state in the United States. Based on these criteria, in June of 1972, a grant award was given to Thayer Hospital by the Maternal and Child Health Service to establish a pediatric dental program in the prescribed geographic areas, with matching funds provided by various local sources. A staff was hired, consisting of a dentist, hygienist, dental assistant, and secretary.

The clinic was designed to serve primarily that portion of the population that historically never received anything except emergency dental care (if even that) — the people whose income falls in that gray area above the state poverty level guidelines (AFDC eligible), and the middle class who can and do provide routine dental care for at least their children. Besides the primary objective of providing dental care services, it was also hoped that this project would accomplish at least some of the following secondary objectives:

1. Demonstrate the effectiveness and practicality of this type of program in a rural setting, and, if necessary, to develop viable alternative approaches to the problem and develop them for the benefit of the public health, social worker, and dental communities.
2. Provide standards and statistics whereby a more accurate insight and appraisal of the nature and scope of dental disease among the poor may be obtained.
3. Provide a complementary background for a dental health education program for utilization by schools and/or community.
4. Provide dental services for children with special circumstances which would otherwise defer a normal treatment regime (i.e., physical, mental, or dental handicaps.)

The clinic began actual operation in July 1972. A large complement of dental services were provided from the beginning — restorative, surgical, and conventional preventive measures, such as fluoride

tablet distribution, topical fluoride application, oral prophylaxes, fissure sealants and oral hygiene instruction. Also included, but only on a very limited basis, were endodontics (only anterior teeth), and space holding orthodontic appliances.

In 1974, the program was expanded to include nutritional counseling for every new family that was seen, endodontic treatment for all teeth where indicated (including molars), and interceptive orthodontics and minor tooth movement procedures. The latter service was made possible by the generous contribution of many hours of valuable time given for consultations by the two local orthodontists, Dr. Charles Cushing and Dr. David Comeau. The clinic hygienist spent many hours from the inception of the program visiting local schools, giving lectures and showing dental education films.

The program was also expanded in other ways in 1974. A survey done in 1973 by Thayer Hospital indicated a need for dental services in Jackman and Bingham. A satellite clinic was established in each town with an additional Maternal Health Grant and staffed by a second hygienist, dentist, and dental assistant, and secretary hired by Thayer Hospital. Originally, the Jackman Clinic was open 2 days a week, and the Bingham Clinic was open 3 days a week. An externship program was instituted with Tufts University School of Dental Medicine in 1974. In this program, a senior dental student spends 9 weeks of his school year treating patients under the direct supervision of the clinic director.

The clinic also co-hosts (with the local dental society) continuing education programs given by Tufts University School of Dental Medicine to local dentists. These programs were instituted to allow private practitioners in rural environments to attend continuing education courses without incurring the excessive expense and loss of working time normally involved in attending a course at Boston (the closest dental school). These programs have been very well received by the local dentists.

EVALUATION OF PROGRAM

Since the program is now in its fourth year of operation, I believe we can obtain a fair evaluation of its effectiveness in meeting its stated objectives. Table 1 shows the total number of appointments seen each year of operation. The number of appointments kept has increased each year — an indication of increasing efficiency due mostly to less administrative time needed as the program progresses.

The primary goal of delivering care to the target

*Director, Dental Clinic, Mid-Maine Medical Center, Waterville, Maine 04901.

TABLE 1

Fiscal Year	# Appts. Scheduled	# Appts. Cancelled	# Appts. Broken (no notice)	# Emergency Appts.	Total Number of Appts. Kept
1972-73	2,732	53	252	152	2,579
1973-74	3,560	210	603	209	2,956
1974-75	4,367	170	598	170	3,769

TABLE 2

Year of Operation	72-73	73-74	74-75
Number of Patients on Waiting List	883	352	250*
Number of new patients seen	523	248	361
Number of patients on routine preventive recall schedule	—	623	900

*As of November 1975, this number was 75.

population has been fulfilled well. This can be seen by considering the number of patients awaiting appointments (Table 2). The clinic began with a waiting list of 883 but after 3 years of operation, the waiting list decreased to 250, while the number of patients on a routine preventive recall schedule has increased dramatically from none at the start of the program to 900 now.

The DMF (diseased, filled, missing) rates are shown in Table 3 (only the Thayer Clinic is depicted due to the short time of operation of the satellite clinics.) From this, one can see that there has indeed been an improvement in the dental health status of the population seen by the clinic.

From an economic viewpoint, the clinic has shown itself to be an economically feasible method of delivering care to children of low income families. A cost analysis was done for fiscal years 73-74, and 74-75 to evaluate the effectiveness in delivering care, utilizing the State schedule of payments for medicaid patients. This showed that the total clinic budget was \$67,059; the State would have reimbursed \$51,509 for services listed, using the medicaid fee schedule as a basis for calculations.

This compares favorably with the State's medicaid contracts with private dentists — there is a 23% difference. There will be a complete cost analysis and evaluation of this program in the *Journal of Public Health Dentistry* within the next few months. But it is important to consider the other services delivered by the clinic which were not included in these figures — prevention counseling, nutritional counseling, fissure sealants, helping to educate dental students, assisting school dental health education programs, and providing a setting in which handicapped or retarded children may receive care. These services are difficult to value objectively but subjectively, they mean a great deal to the families of the patients involved.

As with many state programs today, the first few years of a program are funded by the state, with the funding being substantially reduced after that. This program is no exception and will be expected to attain close to self-sufficiency next year. Various

TABLE 3

	Decayed	Missing	Filled
Patient's initial visit	1,152	134	219
Patient's last recall visit	166	231	1,284

local alternate funding sources are being explored to help meet the costs of the program, but I believe the largest source of funds will be from patient fees collected, based on a sliding-fee schedule adjusted to the total monthly income. This will not only involve the patients' families more in the program (which is always a concern in a "free clinic" setting), but more importantly, will correct what I feel is an unfairness in the present program — families are either eligible for completely free dental care for their children, or they are not eligible for any care — even though the income of two families may only be 10 or 20 dollars different per month. With a sliding fee scale, the poorest families would still receive care, but the relatively more affluent (although still considered low income) would not be penalized for having jobs (albeit, low paying jobs).

PROBLEMS INCURRED

There have been surprisingly few problems incurred with the original program. Initially, some local dentists justifiably expressed concern about the federally funded clinic being established. This fear dissipated shortly after the clinic opened, when it was found that the clinic was indeed only treating patients that previously had not sought dental care — which was its stated purpose. A chief reason for the clinic's acceptance by local dentists and its effectiveness in meeting its goals must be attributed to the close liaison and support of the area dentists. The clinic director meets quarterly with the clinic advisory board, which consists of all area dentists, with four presiding as officers. I feel that besides the obvious advantage of contributing to good relations between the State clinic and private dentists, having the advisory board overseeing the clinic's affairs adds continuity to the clinic program — always a problem in a state clinic where the turnover rate of personnel seems to be innately high. The advisory board, with the clinic director, also has the power to change the emphasis of the program, within the grant guidelines, to effectively meet the continually changing dental environment of the community. I feel this flexibility is of utmost importance in any clinical program if it is to remain effective year after year. This flexibility must be done at the local level,

where local problems are much more apparent than in some regional federal office hundreds of miles away.

It was mentioned earlier that last year satellite clinics were established in Bingham and Jackman in an expansion of the area served by the program. This was the result of various studies evaluating the needs of the area, including an ESPDT (Early Screening, Prevention, Diagnosis & Treatment) program. After 6 months of operation, it became apparent that the services of the Jackman Clinic were not being utilized effectively. The Jackman clinic's time of operation was reduced from 2 days to 1 day per week, while increasing the Bingham Clinic to 4 days per week. The patient load at Jackman has remained far below the expected. Thus, even though the need for dental care is present, the demand for this care is not. A possible solution to this dilemma is a mobile dental unit. For example, after surveys have indicated that the need is present in a given area, then dental education programs could be instituted (such as is being considered statewide now in the legislature) either prior to or concomitant with actual dental corrective treatment. Preferably not only the need, but even more importantly the demand for care in an area should be determined before the expense of establishing a clinic is incurred. It would be feasible to later install a permanent clinic in areas that demonstrate (in a mobile dental unit) demand for care and, just as important, patient motivation to obtain the care and practice good preventive dentistry. Without the latter, it is difficult to justify establishing a corrective program in the first place. I also feel this method could not help but attract private practitioners to areas that

now cannot convince a dentist to settle there. After the State clinic has operated for a time successfully, and the dental I.Q. and demand for services of a local area have increased, a dentist seeking a location would be much more willing to locate there since it would already have been shown that a dentist is in fact needed *and wanted* in the area. Thus the chronic maldistribution of private dentists in the State could be improved indirectly by the clinic program.

SUMMARY

In conclusion, it has been shown that a State-funded dental clinic can be efficient and effective method of providing care for low income families that do not qualify for medicaid programs. I strongly believe one of the major reasons for this clinic's success has been its strong emphasis on the prevention program. These services are of the utmost importance both to the patient and to the clinic. If corrective restorative treatment is provided without an effective prevention program, the clinic will make little or no progress toward the goal of improved community dental health. If good restorative treatment is not built upon a firm foundation of dental education and, perhaps more important, motivation, we then provide a service of questionable temporal value to a few selected patients year after year, while completely ignoring the basic concept of a public health service — to help as many people as possible to maintain good health. We must start emphasizing the importance of dental education and home preventive care in all state clinics if we are to make any progress towards good dental health for the children of Maine.

ENDOMETRIOSIS: TREATMENT WITH DANAZOL — *Continued from Page 48*

pregnancy must be important criteria for making a sound decision in each case. If a decision is made to try a conservative operation in the hope that the patient will conceive, it is important to inform the patient that she may have to undergo a second operation in the future for a permanent solution to the problem.

A new method of treatment has been discussed which appears to offer an important conservative therapeutic approach to the problem of endometriosis. This new drug, Danazol, has been used with a high degree of success by several clinicians with a minimum of side effects.

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Maine Blue Cross and Blue Shield News

PART B PRESENTS PROBLEMS: NABSP

William E. Ryan, President-designate of the National Association of Blue Shield Plans (NABSP), said in recent testimony that "Medicare Part B cannot continue to be regarded as a paid-in-full program and at the same time attempt to control costs" at an unrealistic economic level.

Ryan made the statement before the House Subcommittee on Health of the Committee on Way and Means, which was holding hearings on Medicare issues. He was accompanied by James D. Knebel, Executive Vice President of NABSP.

Ryan observed that the inflationary trend in the economy has caused the original objectives of a paid-in-full program for Medicare to conflict with the need to limit the government's financial liability.

Alluding to the erosion of physician assignments under Medicare as a result of changes in the program physician reimbursement formula, the Blue Shield spokesman warned that shifting to a fee schedule at this time would pose additional "significant problems."

"If the objective is to limit program liability, it (fee schedule) can be set at essentially any level," Ryan continued. "If its objective is to meet the patient's cost in full, it should be related either to income levels or to usual charge levels. To move Medicare to a schedule approximating usual charges would have an additional inflationary impact, in that those physicians who charge more than average would not move down to accept the schedule."

Ryan questioned whether most physicians would participate in a fee schedule program. He said Medicare originally selected the Usual, Customary, and Reasonable (UCR) method because it recognized that a fee schedule did not adequately recognize problems posed by such factors as medical specialization and inflation.

These factors still exist, Ryan pointed out; in fact, the inflationary trend has accelerated in recent years to the point where the use of an economic index has been mandated by the Medicare law.

He summarized his comments on Medicare reimbursements by saying that Congress must choose whether it wants to go with a payment-in-full program or limitation of the government's liability.

"Once a decision is made," he said, "it is only fair to inform the public, the providers of care, and the program administrators of the decision."

On other matters, Ryan made these points:

- Appropriate amendments should be made to the Social Security Act to allow the Professional Standard Review Organization System PSROS to use valid and recognized statistical sampling techniques in their review process, rather than reviewing 100 percent of the cases.
- The January 1, 1976 deadline for Health, Education, and Welfare (HEW) to contract with a professional association to serve as a PSRO should be extended.
- NABSP would be in favor of Medicare coverage for PAP smears — limited to one per year — when it is incident to an office visit.

News, Notes and Announcements

For Members and Guests of the
Woman's Auxiliary

to the
Maine Medical Association
Legislation Day

March 25, 1976
(Alternate "Storm" Date — March 29)

St. Paul's Center
136 State Street, Augusta, Maine

9:30 a.m. Registration
12:15 p.m. Luncheon

Speakers — Meetings with Representatives
Afternoon Tour of State House

For Luncheon Reservations, by March 19
Write: Mrs. Raymond Culver, 91 Silver Street,
Waterville, Maine 04901.

Postgraduate Course for Emergency Physicians

The Maine Medical Center will again sponsor and run a postgraduate course for emergency physicians in April 1976.

Brochures will be sent to emergency rooms throughout the State in the near future from the Maine Medical Center.

County Society Notes

Androscoggin

The Androscoggin County Medical Society held its regular meeting at Steckino's Restaurant in Lewiston, Maine on September 18, 1975, with 44 members present. Following call to order at 8:00 p.m. by the President, Dr. Louis N. Fishman, two guests were introduced, Dr. Bausch, newly-arrived internist with specialty in infectious disease, and Dr. Mangees, newly-arrived Emergency Care physician who will be transferring membership from the State of Pennsylvania.

The minutes of the April and May meetings were reviewed and approved. Multiple types of correspondence throughout the summer months reviewed by the President and the Secretary.

Names of Drs. In Guk Kim and Paul Atallah were presented for application for membership. They will be reviewed by the Credentials Committee, and submitted for vote of the membership at the October meeting.

Dr. Fishman had also received a communication from Mr. Dunlap, Chairman of the City of Lewiston Disaster Committee, requesting that the County Medical Society assist in establishing a volunteer triage team. This was approved by the membership, and Dr. Fishman will meet with the Lewiston Disaster Commit-

tee to implement this request. Following a discussion of the mandate of the President of the Maine Medical Association to establish County-wide mental health care committees, Dr. Fishman indicated that he would appoint such a committee, should the psychiatric members of the Society be willing to serve.

There being no old business, the meeting progressed immediately into new business, at which time Dr. Thomas F. Shields reviewed the proceedings of the House of Delegates in June. Considerable discussion was centered about the continued lack of visible action dealing with the Medical Liability Commission and the complete lack of influence that individual County members seem to have on the legislation process. Dr. Ross Green submitted a letter of resignation from the Legislative Action Committee and requested that the functions as carried on by the Legislative Action Committee be delegated to the delegates to the State Medical Association in bringing the Society's wishes to its parent organization at the Interim House Meetings. Dr. Fishman accepted the letter of resignation with regret.

There being no further business to conduct, the meeting was adjourned at 9:10 p.m.

RICHARD M. SWENGEL, M.D., *Secretary*

Letters to the Editor

To the Editor:

The October 1975 issue of *The Journal of the Maine Medical Association* contains an article by Taylor and Onion entitled "The First Six Months after Otitis Media." The first paragraph of this article makes the startling statement that 24% of their series of otitis media had a transient hearing loss. This would lead to the obvious conclusion that the 76% of their cases without hearing impairment were misdiagnosed, until further in the article it is disclosed that their criteria for hearing impairment was based on a screening test carried out at 30 decibels!

Nowhere in the article is there any evidence that the authors ever heard of myringotomy, a procedure as important in the treatment of otitis media as the use of antibiotics.

The authors advance some rather dubious statistics regarding sex linkage and the occurrence of otitis media and the recurrence rate of the compliant versus the non-compliant group in the taking of the prescribed medications, the compliant group having a fivefold greater recurrence rate than the non-compliant group. One wonders by what quirk of logic the authors were led to believe that the parent who was non-compliant in the administration of the child's medication would be any more reliable in returning the child for medical attention at the next sign of re-

currence. Many parents will ignore an earache in the night that is gone by morning, and will not recognize otorrhea until it drips onto the collar.

Dan, it bothers me to see this kind of article in our Journal. It is of absolutely no scientific value and can only serve to tarnish the reputation of *The Journal of the Maine Medical Association* as a serious scientific publication.

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Primary Carcinoma of the Duodenum

A Case Report†

CHARLES W. STEELE, M.D.* and WALDO A. CLAPP, M.D.**

Kleinerman et al¹ stated that the first report of a case of primary carcinoma of the duodenum was found among the writings of Geoginis Hanberger² as early as 1746 and a second instance was recorded by Giovanni Morgagni in 1761. Almost a century elapsed before additional cases were recorded. Case reports then began to appear after the turn of the 19th century. Nevertheless, primary carcinoma of the duodenum remains a relatively rare type of malignancy having a reported instance of 0.03 to 0.003 percent of all autopsies, or 1 in 300 to 1 in 31,000 autopsies. Berger and Koppleman³ in 1942 reported one intrapapillary primary carcinoma of the third portion of the duodenum. Their careful review of the literature up to that date, including their case, brought the number of acceptable instances of carcinoma of the duodenum to 386; of this number, 58 or 15 percent were intrapapillary. Brenner and Brown,⁴ in their comprehensive review of the literature, reported that 438 authentic cases of duodenal cancer had been reported up until April 1948 of which 18.3 percent were located in the intrapapillary portion of the duodenum; and they found that 21 more acceptable cases had been reported in the literature, mostly as isolated instances. They added an additional 15 cases of their own bringing the 1955 totals up to 472. Seven out of their 15 cases were located in the intrapapillary or third part of the duodenum. Iovine and Tsangaris⁵ reported in 1961 that only 598 cases of primary adenocarcinoma of the duodenum had been documented and added 4

more cases bringing the total to 602. Moss et al⁶ reported in June 1974 that only 602 cases of duodenal carcinoma had been recorded through 1960⁵ and that this type comprised 33 percent to 45 percent of all small intestinal tumors. Moss and his group⁶ reported 8 additional cases of which 5 tumors, or 62 percent, were noted to have originated in the intrapapillary or third portion of the duodenum. Clapp and Haas⁷ in 1970 saw and operated on 1 additional very rare case with von Ricklinghausen's disease who developed a neurofibrosarcoma of the duodenum. This was, to their knowledge, only the fourth such case documented in world literature.

We wish to present one additional case of primary carcinoma of the intrapapillary, or third portion, of the duodenum.

A CASE HISTORY

This is a case history of a 73-year-old retired Air Force Colonel. This man abruptly became symptomatic from his last illness on April 10, 1973 almost immediately after he had swallowed two mouthfuls of luncheon meat which he did not think was good. He became nauseated almost immediately, retched several times and finally induced vomiting by putting his finger down his throat. Immediately thereafter, he lost his appetite and began to have "gas" after eating, usually retched and regurgitated a little of the food he had just eaten. There was considerable upper abdominal discomfort, but he had no diarrhea, no melena and no other lower gastrointestinal symptomatology.

When he was seen at the office on April 12, 1973, he had a blood pressure of 130/90 on the right and 148/90 on the left, weighed 155 pounds and his color was good. The nasopharynx and neck, heart and lungs were normal. Inspection of the abdomen showed what appeared to be considerable distension involving primarily the upper half of the abdomen. On palpation, this distended area of the abdomen was tender, tympanitic to percussion and felt like a dilated stomach. No tumor masses could be identified and there was no involuntary muscle spasm. The lower abdomen was not distended and seemed normal. A rectal examination did show some impacted feces which was broken up. He was put on liquids and a soft, low residue diet, and was instructed to take antacids one and three hours after meals and at bedtime.

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He was seen again two weeks later on April 24, 1973 at which time he reported no more difficulty with constipation or impaction. However, he had not been able to eat much, had trouble swallowing food and had noted that he had borborygmus at night. Each time he tried to take food, he had not felt "right" and had experienced almost constant "heartburn." He had not regurgitated or vomited food, but he reported retching and gagging frequently after the first visit during which he often got up small amounts of yellowish-brown stomach contents consisting of brownish colored liquid and mucoid material. His weight had not changed. Physical examination on his second office visit showed abdominal peristalsis to be essentially normal, but his upper abdomen and stomach were still definitely distended. This was confirmed by a flat plate of the abdomen taken on the same day at the X-ray Department of the Central Maine General Hospital in Lewiston, Maine. Again no abdominal mass could be palpated and his rectal examination was negative. The color of his feces was a normal brown. He was scheduled for a barium swallow and a barium meal with instructions to eat or drink nothing after midnight on the following day.

This patient was admitted to the Central Maine General Hospital early on the morning of April 26, 1973 and was sent to the X-ray Department where a Levine tube was passed. Five hundred ccs. of gastric contents were removed by suction from the stomach. A swallow of barium showed a small, intermittent, sliding type of esophageal hiatus hernia and a diverticulum arising from the second part of the duodenum. (Similar findings had been previously demonstrated by a barium meal study done on December 17, 1971.) The barium passed readily from the stomach into the normal-appearing proximal portion of the duodenum, but obstruction was encountered at the junction of the second part with the third part of the duodenum (Fig. 1). The duodenal diverticulum was eventually identified with difficulty in the second portion of the duodenum. After 90 minutes, some barium was seen to pass into the distal part of the duodenum just below the level of the diverticulum. At this point, an annular constrictive-type of lesion measuring at least 3 cm. in length was demonstrated (Fig. 2). The remaining portion of the distal duodenum was seen to be normal. The x-ray findings were interpreted as indicating an annular tumor mass in the duodenum large enough to cause intestinal obstruction. A follow-up film at 6 hours revealed some minimum barium passing into the upper small bowel, but most of the barium still remained in the stomach. A supine view of the abdomen 24 hours later revealed only minimal barium remaining in the stomach which was once again seen to be somewhat distended. The remaining barium had passed through the small bowel and the head of the barium column had reached the large bowel.

The past history was essentially negative except for an appendectomy and a TUR. He had been found to have a mild hypertension the year before and was receiving 50 mgs. Hydrodiuril and 0.25 mgs. of Reserpine daily for this condition.

All admission laboratory findings were normal except for a mild elevation of the BUN (Tables 1 and 2).

The patient was transferred to the private surgical service of the second author who first had him duodenoscoped. This revealed a friable mass with a 3 mm. ulceration on its top surface which was obstructing the small bowel at the junction of the second and third segments of the duodenum. A biopsy specimen was taken from the ulcerated area and saline washings from the entire lesion were collected and sent to the Pathology Laboratory for a cell block and section. The ampulla of Vater was not visualized, but significant bile reflux was encountered to suggest that the ampulla lay proximal to the tumor lesion.

Pathology reported that the biopsy specimen consisted of two minute fragments of rubbery, pinkish-tan tissue varying from 2-6 mms. in greatest diameter. Sections of the two biopsy fragments showed the lining epithelium and a gland to be benign. The lamina propria was infiltrated with varying numbers of round cells, plasma cells and macrophages. There was no evidence here of specific inflammatory granulomatous infiltrate or neoplastic disease.

The second specimen, labeled duodenal washings, contained several small fragments of soft, friable, tannish-red tissue weigh-



Fig. 1. Barium Meal reveals partial obstruction of the duodenum at the junction of the second and third portions with considerable delayed passage of barium into the small bowel.

ing less than one-quarter gram. Sections of the cell block from the specimen labeled duodenal washings showed a sheet of atypical cells with the following features: hyperchromatic, pleomorphic nuclei; variable amounts of lightly eosinophilic granular cytoplasm and indistinct cell borders. There was no evidence of glandular differentiation (Fig. 3). The origin of these cells was not clear to the Pathologist. It was thought they probably represented poorly differentiated malignant epithelial cells. Also identified were fragments of benign small bowel mucosa.

This man was accordingly prepared for surgery and an exploratory laparotomy was done on May 3, 1973. Upon opening the peritoneal cavity, a moderately dilated stomach was encountered which carried through the first and second portions of the duodenum; however, at the junction of the second and third portions of the duodenum there was a firm, fixed, hard, indurated mass which was densely adherent to the retroperitoneal structures including the superior mesenteric artery. Because of this, any attempt at mobilizing the duodenum in this area was deemed unwise. The duodenum, distal to this area, again resumed its normal size and contour. Not only did this lesion extend to the lower pole of the right kidney by direct continuity, it also extended by direct continuity to the mesentery of the hepatic flexure with serosal involvement of the hepatic flexure of the transverse colon. The foramen of Winslow was patent. There were large nodes palpable along the hepatoduodenal ligament. The common bile duct was not visibly dilated. It appeared that the ampulla of Vater would be higher than the origin of the tumor. The head of the pancreas appeared to be in close approximation to the previously described growth; however, there were no nodules palpable in the head of the pancreas nor along its body or tail. There were no palpable nodes in the liver and no areas of peritoneal seeding other than that described to the transverse mesocolon. The gallbladder showed no evidence of pathology.



Fig. 2. Spot films of the duodenum demonstrate a 3 cm. annular constricting lesion at the junction of the second and third portions of the duodenum.

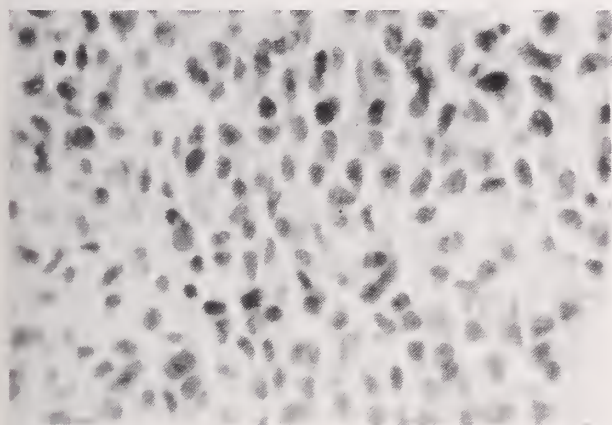


Fig. 3. Microscopic finding on section of cell block from duodenal washings.

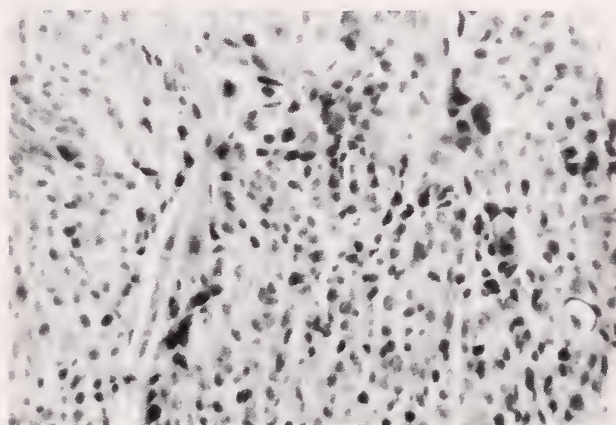


Fig. 4. Microscopic appearance of cell in lymph node biopsy taken at operation.

Palpation of the remaining colon, spleen, left kidney and remaining large bowel was negative.

It was decided at the time of operation that the tumor was not resectable. Therefore, the hepatic flexure of the transverse colon was separated from the anterior aspect of this growth. A biopsy specimen was removed from the transverse mesocolon where the tumor had spread by direct extension. An anterior gastroenterostomy was performed using two layers of interrupted black silk for the serosa and a continuous lock stitch of 00 chromic for the

muscularis mucosa. At the end of the anastomosis, the stoma admitted the tips of three fingers with ease. Hemostasis was found to be complete. The omentum was brought down over the small bowel and the abdomen was closed in anatomical layers. The patient's postoperative condition was good.

The biopsy specimen removed from the transverse mesocolon where the tumor had directly extended was reported by the Pathologist as consisting of two small, rubbery, pinkish fragments of tissue varying from 2-6 mms. in greatest diameters.



Fig. 5. Follow-up study reveals a normally functioning gastrojejunostomy stoma with some reflux of barium into the third portion of the duodenum. Obstruction appears to be relatively complete at the lesion.

Section revealed two fragments of fibrofatty tissue extensively infiltrated and replaced by malignant epithelial neoplasia. This was characterized by small nests of cohesive cuboid or squamoid cells having distinct cellular margins and varying amounts of polychromic cytoplasm. The smaller cells had small, round, centrally located vesicular nuclei. The larger cells had huge markedly pleomorphic, irregular nuclei. Lymphocytic invasion was conspicuous (Fig. 4). A primary site for the metastasis was not obvious. The neoplasm appeared more epidermoid than glandular. Pathological diagnosis: anaplastic carcinoma.

This man made an uneventful recovery postoperatively. He was then seen by J. A. Leonardi, M.D. of the Nuclear Medicine Department of the X-ray Department of the Central Maine General Hospital who felt that in view of the spread of the tumor which was demonstrated at the time of operation, radiation therapy would not be indicated and would only result in clinical symptoms and distress. The reason for this opinion was that in order to include the full extent of the disease a large portal would be needed and a deep dose would have to be used which would result in exceeding the tolerance level for the small bowel. All other members of the Nuclear Medicine staff concurred in this opinion that cobalt or any other form of deep radiation was not indicated. Therefore, this man was discharged home on May 11, 1973. He was put on a progressive sippy diet and given Valium® prn for anxiety. The clinical diagnosis at the time of discharge was annular adenocarcinoma of the duodenum with extension to the right kidney, to the hepatic flexure of the colon and to the retroperitoneal lymph nodes.

This patient was seen postoperatively by Ronald J. Carroll, M.D., Oncologist at the Maine Medical Center in Portland, Maine, who recommended that this man receive weekly injections of one gram of 5FU. The first dose was given by Dr. Carroll

on June 4, 1973. Thereafter, weekly injections of one gram of 5FU were given by Dr. Waldo Clapp in Lewiston. This patient's blood count remained satisfactory after the first four injections were given, but after the fifth injection was received, he became nauseated, began to vomit and feel sick all over. He was seen immediately and a blood count obtained which showed a drop of the white cell count (Table 1). This man was re-admitted to the Central Maine General Hospital in Lewiston, Maine on July 2, 1973. He was immediately put on antibiotics in the form of Keflin® 2 grms. every 6 hours for 3 days and then 250 mgs. 4 times a day. Daily blood counts were taken (Table 1). A patient profile on July 2nd and another on July 3rd showed all tests normal including bilirubin with the exception of low calcium, phosphorus and total protein (Table 2). The admission urine examination was negative. X-ray examination showed a normally functioning gastroenterostomy with little change in the duodenal lesion (Fig. 5). His leukopenia and his polymorphonuclear cells had improved sufficiently to permit him to be discharged home on July 13, 1973 (Table 1).

After discharge from the hospital on July 13, 1973, this patient did well for only about 10 days. Then he again developed pain in his right abdomen and hiccoughs. Because of the discomfort, poor appetite, weakness and a blood count of 16,500 (Table 1), weekly injections of 1 gram of 5FU were again started on August 6, 1973. After two such weekly injections, he had increased nausea, inability to eat and by August 17, 1973, his blood count again had dropped to 1,200 with a hemoglobin of 9.8 grams and an hematocrit of 29.5 percent. The polymorphonuclear cell count was 46 percent with 9 percent stabs (Table 1). His patient profile showed a low calcium of 7.7 mgs%, a low sodium of 134 MEQ/L, and a BUN of 34 mgs% (Table 2). All the other tests including the bilirubin were normal.

He was accordingly rehospitalized on August 17, 1973 at 2:45 P.M. Physical examination showed a pale, anemic (Table 1) 73-year-old male who had lost weight and showed moderate inelasticity of his skin. No cervical, axillary, or inguinal node adenopathy was present and there was no icterus of the skin or sclerae. The abdomen was moderately distended with a right upper quadrant operative scar well healed. There was a palpable mass in the paraumbilical area which was extremely tender. The liver margin was not palpable because of the extreme tenderness of the mass in the right abdomen. Peristaltic sounds were moderately hyperactive, but there was no evidence of abdominal ascites. Rectal examination was normal and the stool brown. Skin rashes were not seen. All the rest of the physical examination was normal. Diagnoses on this admission were:

- 1) Status postoperative carcinoma of the duodenum with gastroenterostomy therefore,
- 2) Anemia secondary to chemotherapy and marked leukopenia due to chemotherapy with 5 FU.

After admission, one unit of blood was given and Keflex® 250 mgs. po q.i.d. was begun. Compazine® was given for nausea. He had severe hiccoughs after admission and Thorazine® 25 mgs. 1M was given. Blood counts at this admission are shown in Table 1 and the results of the patient profiles in Table 2. The temperature remained near normal until August 23, 1973 when it suddenly rose to 107 rectally. The leukopenia gradually grew more severe until the white count had dropped to 500 on August 21, 1973 (Table 1). His BUN rose to 54 mgs%. He did not vomit, did not have any melena, and had no gross gastrointestinal bleeding. He deceased 6 days after admission. Permission for postmortem examination was not obtained.

The final clinical diagnoses were:

- 1) Annular adenocarcinoma of the duodenum of 4 months' duration,
- 2) Agranulocytosis due to chemotherapy with 5FU,
- 3) Anemia, normocytic.

DISCUSSION

The diagnosis of a primary neoplasm of the duodenum has been one of the most difficult encountered in the field of medicine. Tumors arising in the infrapapillary, or third part of the duodenum, are

TABLE 1

COMPLETE BLOOD COUNTS

DATES 1973	WBC	RBC	Hemoglobin	Hematocrit	MCV	MCH	MCHC	Polys	Stabs	Lymphs	Monos	Eos	Basos	Myelocytes	Meta- myelocytes	Platelets	Reticulocytes	Anisocytosis
26 Apr	10,600	5.27	16.3	46.3	89	31.1	35.3	86	1	16	3					402,000		
2 May	6,200	5.05	15.2	43.2	86	30.2	34.4	64	2	24	5	5						
11 June	9,200	4.3	12.6	37.2	86	30	34.9	48	4	39	4	4	1			375,000		
18 June	8,400	4.41	13.2	38.5	87	30.5	35.2	53	1	42	4	1				normal		
25 June	6,200		13.2	38.8				49		45	2	4				normal		
2 July	1,600	4.66	13.3	40.7	87	31.4	36.1	18	8	19	2	3				normal		
3 July	1,100	4.07	12.3	35.1	86	31.1	30.1	4	0	88	6	2				153,000		slight
4 July	1,400	3.79	11.3	33	87	30.4	35.7	4	0	90	4	2				normal		
5 July	1,600	3.44	10.3	29.7	86	31.1	36.1	14		77	4	5				152,000		1+
6 July	1,300							61	4	18		7				normal		slight
9 July	6,100	3.40	10.1	29.3	86	30.4	35.8	21	10	35	10	5	2	2	15	normal		1+
6 Aug	16,900		11.6	32.8				78		10	4	8				304,000	1.5	GGT 25
13 Aug	17,900	3.36	10.4	31	91	31.1	34.9	80	1	17	1	1				normal		1+
17 Aug	1,200	3.2	9.8	29.5	88	30.4	34.6	46	9	38	7					normal		1+
18 Aug	600	3.4	10.4	30	88	30.1	35	12	2	86						normal		1+
19 Aug	500	3.5	10.8	32	88	30.8	35	5		76	18	2				normal		
20 Aug	800	3.52	11.1	31.4	86	31.5	36.5	8		86	5	1				normal		
21 Aug	500							10	2	84	3	1						1+

**

** Deceased August 23, 1973.

TABLE 2

PATIENT PROFILES

DATES 1973	TEST NORMAL RANGE	Calcium 9-11 mgs%	Phosphorus 2.5-4.5 mgs%	Glucose 65-110 mgs%	BUN 10-20 mgs%	Uric acid 2.5-8 mgs%	Cholesterol 150-300 mgs%	Total protein 6-8 gms%	Albumin 3.5-5 gms%	Total bilirubin 0.15-1 mgs%	Alkaline phosphatase 30-85 mU/ml	LDH 100-225 mU/ml	SGOT 7.5-45 mU/ml	Chloride 100-108 MEQ/L	Venous bicarb. 24-28 MEQ/L	Sodium 138-146 MEQ/L	Potassium 3.8-5 MEQ/L	Venous PH 7.35-7.45	PCO ₂ 35-50 MMHG	Creatinine 1-2 mgs%	Serum globulin 2-3 mgs%	Phosphohexoisomerase 20-90 IU/L	PTT 25-35 seconds	Prothrombin time 11-15 seconds	Lipase
26 Apr	10.8	4.8		60			8.4							89	32	140	4.2	7.480	43.5		3.5	38	28.5	12	
27 Apr	11.3	5.1	145	63	12	260	8.3	5.5	0.8	77	193	10								3.1					
30 Apr				33													3.5			2.5					
2 May				26	12.6		6.7							93	36	137	3.7	7.508	46.1		2.8				
3 May				93																					
7 May																									
2 July	8.1	2.1												97	27	140	4.6	7.426	42.1		96				
3 July				155	34	6.5	150	5.7		1.4	55	150	7.6	99	21	134	3.8	7.475	29.2					13	
17 Aug	7.7	3.5																							86
20 Aug				190	54	7.8	130	5.6		0.7	80	145	5												

even harder to diagnose preoperatively. In the older reviews and summaries of the literature, carcinoma of the third portion of the duodenum comprise, according to Brenner and Brown⁴ 18.3 percent and to Berger and Koppleman³ 15 percent of all carcinomata of the duodenum. Chodoff et al⁸ in 1953 stated that it is possible with better techniques to make this diagnosis preoperatively. They reported one such case of carcinoma of the intrapapillary portion

of the duodenum diagnosed by x-ray preoperatively who lived seven and a half months after resection of the tumor followed by an end-to-end anastomosis of the remaining portions of the duodenum to the upper jejunum anterior to the superior mesenteric vessels. More recent reports^{5,9,10} suggest that the treatment of duodenal carcinoma is surgical excision whenever possible and that pancreaticoduodenectomy is the operation of choice. All authors

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agree that the survival rate is usually limited to a few months for those patients with inoperative duodenal tumors, and, therefore, they must be treated palliatively.

Our case had primary carcinoma of the infrapapillary portion at the junction of the second and third parts of the duodenum. The lesion was diagnosed preoperatively both by x-ray and by duodenoscopy, and confirmed microscopically from the section of a cell block made from duodenal washings collected through the duodenoscope. The outstanding early clinical signs and symptoms were the sudden onset, loss of appetite, inability to eat, almost constant nausea accompanied by retching and the spitting up of small amounts of gastric secretions and small amounts of food. Later major signs and symptoms were the constant nausea, some vomiting, pain and soreness in the right upper quadrant, prolonged constant hiccoughs, and a palpable tender mass in the right upper quadrant and grossly audible borborygmus. Diagnostically significant was the absence of jaundice and the normal bilirubins.

Operation confirmed the presence of an annular adenocarcinoma at the junction of the second and third sections of the duodenum with almost complete obstruction of the bowel, and showed the

tumor mass to be densely adherent to the retroperitoneal structures including the superior mesenteric artery and extension to the lower pole of the right kidney, the mesentery of the hepatic flexure and transverse bowel by direct continuity. There was serosal involvement of the hepatic flexure of the transverse colon. There were large nodes palpable along the hepatic ligament, but the common bile duct was not visibly dilated. It appeared that the ampulla of Vater was higher than the origin of the tumor. The head of the pancreas was in close approximation to the tumor, but there were no palpable nodules in the head of the pancreas nor along its body or tail. There were no palpable nodules in the liver and no peritoneal seeding. The gallbladder showed no pathology. The tumor was not removable. All that could be done surgically was to perform a palliative anterior gastroenterostomy.

Since radiation therapy was deemed inadvisable, this patient received chemotherapy in the form of 1 gram of 5FU every seven days for a total of five injections when these injections had to be left off because of severe leukopenia and agranulocytosis. The second series of weekly injections of 1 gram of 5FU was begun four weeks later, but again had to be stopped after the second weekly injection because of severe leukopenia and agranulocytosis.

This chemotherapy had no demonstrable beneficial effect on the primary intrapapillary tumor of the third segment of the duodenum or on the metastasis; but it did cause serious depression of the bone marrow, increased undesirable hard-to-bear symptomatology, and may have been responsible for the lowering of serum calcium and total serum protein and for the rise in blood urea nitrogen. Cortese and Cornell¹¹ report that radiotherapy, except in the management of lymphomatous disease, has little to offer in the therapy of duodenal malignancy, and that the use of cytotoxic chemicals in this disease may be of palliative value in the inoperative or unresectable patients or in patients with recurrent disease. Our experience with the cytotoxic chemical, 5FU, was determined to be that it was of no value in this case of adenocarcinoma of the intrapapillary, third part, of the duodenum.

SUMMARY

One case of primary annular adenocarcinoma at the junction of the second and third portions of the duodenum is presented. The case was inoperable and unsuited for any kind of deep x-ray or cobalt treatment. Chemotherapy using 5FU was given, but without any apparent beneficial effect as far as the tumor or its metastases were concerned. There was production of a severe leukopenia and agranulocytosis which on two occasions was severe

enough to necessitate termination of the chemotherapeutic agent.

ACKNOWLEDGEMENT

The authors wish to thank Dr. John W. Carrier, chief of x-ray at Central Maine General Hospital, for preparing the photographs of the duodenum used in this paper and to Dr. Robert J. Sbaschnig, associate pathologist at Central Maine General Hospital, where the preparation of the photographs of the duodenal washings and of the lymph node removed at the time of surgery.

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Benefits of BEROCCA TABLETS

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A Preliminary Report

VICTOR M. PARISIEN, M.D.* and PAUL M. BEEGEL, M.D.**

This is a survey of the patients being actively followed at the Scoliosis Clinic of Central Maine General Hospital up to April 1975. One hundred ninety-seven patients were followed of which 50 were male, an incidence of 3 females to one male. This ratio is lower than generally reported (Moe 5.5:1, Goldstein 8:1).

Sixty-seven patients were treated with the Milwaukee Brace and an exercise program following the techniques of Blount and Moe (Blount, W. P. and Moe J. H. The Milwaukee Brace, Williams & Wilkins Co., Baltimore 1973).

The results of treatment are shown on Table 1.

SCOLIOSIS CORRECTION

no. of patients in brace	67	100%
improved	22	32%
maintained	13	20%
worsened	32	48%

The average correction obtained was 44.8%.

Percentage of correction = $\frac{\text{Degrees of correction}}{\text{Degrees of original curve}} \times 100$.

Forty-three curves were studied in this group.

Table 2 shows the correction obtained in kyphosis.

KYPHOSIS CORRECTION

no. of patients in brace	18	100%
improved	15	83%
maintained	3	17%

One hundred and thirty patients were followed with serial x-rays. Their curves were not judged severe enough nor progressive enough to be treated with the brace.

no. of patients	130	100%
improved	56	43%
maintained stable	63	48%
worsened	11	9%

The following parameters were studied and ana-

lyzed by the Chi Square method as to their effect on the amount of correction obtained.

1. number of years in brace	not significant
2. number of years observed — no brace	not significant
3. age when first seen and put in brace	not significant
4. age when first seen — no brace	not significant
5. position of primary curve — dorsal, dorso lumbar or lumbar — in brace	not significant
6. position of primary curve — dorsal, dorso lumbar or lumbar — no brace	not significant
7. cooperation with exercises in brace	not significant
8. cooperation with exercise — no brace	highly significant
	Chi Square 11.67
	— significant to 0.05

Thus, the only significant parameter which was found to influence the amount of correction obtained was the degree of cooperation in an exercise program as judged by the treating physical therapist. The extent to which the exercises were done, if at all, and the skill attained in performing them were estimated at regular visits to the physical therapy department. Those who were judged to do their exercises and do them well achieved significantly better results in either maintaining their curves stable or in actually obtaining correction, than those who did not.

Spontaneous improvement is known to occur in at least 22.4% of patients (H. L. Brooks, S. P. Azen et al Scoliosis: a prospective epidemiological study J.B.J.S. 56-A/7 Oct. 1975, 968-972) but even if this is taken into account, the results were better in those patients who did their exercises assiduously.

The brace was found to be more effective in correcting kyphosis than in correcting scoliosis. This is in agreement with the experience of others in this field.

Maintaining a curve stable until maturity is a desirable effect obtainable with the brace, so that, overall 52% satisfactory results were obtained with its use.

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The "Cervical Syndrome"*

VICTOR M. PARISIEN, M.D.**

One hundred and thirty patients were seen for "cervical syndrome" in the last four years. Of these, 25 were lost to follow-up, leaving 105 patients with a follow-up of at least three months.

The "Cervical Syndrome" referred to in this report is a clinical concept, not a diagnosis and denotes a condition characterized by pain and stiffness in the neck. There is usually radiation to one or both shoulders, the upper dorsal or interscapular area and frequently, accompanying headache. The pain seldom radiates below the elbow in distinction to frank disc herniation. There may be associated dizziness, visual disturbances such as a rushing or plopping sensation in the ears. The onset may be gradual and spontaneous, or acute as the result of a sudden effort as in stumbling or lifting. It is frequently caused by acceleration-deceleration (whiplash) as seen in vehicular accidents especially rear end collisions.

Pain

The pain is usually related to motion with consequent splinting of the neck muscles in protective spasm. It is usually described as aching or pressure which may be dull or moderate to severe. There is often a burning sensation.

Stiffness

Stiffness of the neck as evidenced by diminished range of motion is characteristic and is largely due to muscle splinting and increases and decreases along with the pain. This is often radiologically demonstrable as straightening or diminished flexion of the cervical spine. Often the pain and stiffness are worsened by a drop in barometric pressure. Tenderness to palpation is usually found and correlates well with the area of pathology seen on the x-ray. It can be elicited at the interval between the spinous processes, at the facet joints and in the paravertebral musculature. Often "trigger areas" are found, that is tender firm nodules in the muscles beneath the fascia from which pain radiates on pressure.

X-ray

The changes seen on x-ray include disc interspace narrowing, anterior, posterior, and posterolateral osteophyte formation in the uncovertebral joints of Luschka. These changes increase in frequency and severity with increasing age. Diminution of flexibility as seen on flexion-extension views of the neck

TABLE 1

Group I			Group II		
Classification	#pts.	%	Classification	#pts.	%
Failure	48	66.6	Failure	8	16.6
Good	17	23.6	Good	11	22.9
Very Good	7	9.7	Very Good	29	60.4
Total	72		Total	48	
Total Good & VG	24	33.3	Total Good & VG	40	83.3

TABLE 2

ACUTE 42 patients			CHRONIC 65 patients		
Group	# pts.	Ave. Time of Symp.	Group	# pts.	Ave. Time of Symp.
I	35	15.6 days	I	37	15.8 weeks
II	14	11.0 days	II	34	18.5 weeks

and straightening of the lordosis are associated with stiffness and muscle spasm. This study involves a comparison of two modes of therapy. Group I was treated with "standard" forms of therapy. Acute cases were given a foam collar, diazepam 5-10 mg tid and analgesics. If no improvement occurred in two weeks, self-applied home cervical traction was used for 20 minutes tid, initially with 5 lbs. and increasing as tolerated to 15 lbs. Patients were instructed in isometric neck exercises. If trigger areas were found, these were treated with ultrasound or steroid injections.

Group II was treated with electrical stimulation of stainless steel needles placed through the skin and into ligaments or muscles at predetermined points.

Group I comprised 72 patients, group II 48 for a total of 120. Fifteen patients were transferred from Group I to Group II after failure of treatment in group 1.

Since pain is the main consideration, the following method of pain assessment was chosen. Patients are asked to rate their pain relief as a percentage of the original pain. Zero to 50% pain relief is classified as a failure, 50-80% relief is classified as good and 80-100%, i.e., no pain is classified as very good.

Overall results were tabulated in Table 1.

Chronicity of Symptoms

A somewhat arbitrary cut-off time of six weeks was determined to classify acute versus chronic duration. Patients in the acute category are expected to fare better than those with chronic symptoms. The results are in Table 2 indicating that there was not a preponderance of acute patients in group II. Indeed there were more patients with chronic duration of symptoms in group II and the duration of their symptoms was longer on the average.

It was also noted that the chronicity of the symp-

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toms did not mitigate against a successful result in group II patients.

Recovery Time

Time to recovery was assessed for those who improved. It was 13.7 weeks average for group I and 5.1 weeks for group II. For those with no improvement, group I patients were treated an average of 16 weeks, group II an average of 3 weeks.

Age

The average age of patients was 40.2 years.

	ACUTE	CHRONIC
Group I	32.2 yrs.	47.1
Group II	38.8 yrs.	42.9

X-ray Changes

Fifty-six patients had x-ray changes as delineated above. Twenty-two patients had normal x-rays, 13 patients had segmental straightening of the cervical spine with otherwise normal x-rays.

The frequency of degenerative disc disease as found in this group of patients correlates well with their age; the older patients having the most severe changes often with involvement of more than one level. The changes in many cases were undoubtedly present before the precipitating trauma. There is perhaps a greater susceptibility to cervical syndrome when pre-existing degenerative disc disease is present.

TABLE 3

RESULTS IN PATIENTS WITH D.D.D.					
Group I			Group II		
Classification	#pts.	%	Classification	#pts.	%
Failure	18	60.0	Failure	5	19.0
Good	10	33.3	Good	9	34.6
Very Good	2	6.7	Very Good	12	46.1
Total	30		Total	26	
Total Good & VG	12	40.0	Total Good & VG	21	80.7

TABLE 4

RESULTS IN PATIENTS WITH NORMAL X-RAYS					
Group I			Group II		
Classification	#pts.	%	Classification	#pts.	%
Failure	6	50	Failure	2	22
Good	4	33	Good	1	11
Very Good	2	16	Very Good	6	66
Total Good & VG	6	49	Total Good & VG	7	77

No significant difference in results was shown in group II patients who had normal x-rays. On the whole, the results were just as favorable whether or not x-ray evidence of D.D.D. was present. Slightly better results were obtained with group I treatment in patients with normal x-rays. This finding is not considered to be significant because of the small number of patients.

A high percentage of degenerative disc disease was found. In the 40-50 age group, 83.4% had x-ray changes compared to the expected incidence of 25%

in asymptomatic people (Friedenberg & Miller JBJs 45 A 1171 Sept. 63). In the 30-40 age group, 47.8% had x-ray changes compared to an expected incidence of 5%. In most cases, these changes pre-date the onset of symptoms, although in a few cases the x-ray changes were seen to begin while the patient was under observation. The presence of D.D.D. may thus predispose to the development of the cervical syndrome.

PRESENCE OF D.D.D. ON X-RAY

Age	D.D.D.	Normal	%	Expected % (asymptomatic)
10-20	2	4	33	
20-30	2	13	13.3	
30-40	9	10	47.8	5
40-50	15	3	83.4	25
50-60	14	2	87.5	70
60-70	4	0	100	75
70-80	2	0	100	

Litigation

Forty-four patients were involved in litigation. Eighteen had been involved in automobile accidents. An additional eighteen had been in cars which were hit from behind by another vehicle. Eight had claims pending before the Industrial Accident Commission.

Of the 18 patients involved in rear end collisions, 9 were in group I and 9 in group II.

All the group II patients were rated very good. Six of the group I patients were rated good and 3 were unimproved.

TABLE 5

REAR END COLLISIONS			
Group I		Group II	
Classification	#pts.	Classification	#pts.
Failure	3	Failure	0
Good	6	Good	0
Very Good	0	Very Good	9

Of the 18 patients involved in other car accidents, the results are tabulated in Table 6.

TABLE 6

OTHER VEHICULAR ACCIDENTS			
Group I		Group II	
Classification	#pts.	Classification	#pts.
Failure	5	Failure	0
Good	4	Good	4
Very Good	2	Very Good	3

TABLE 7

OF THE 8 INDUSTRIAL ACCIDENT PATIENTS			
Group I		Group II	
Classification	#pts.	Classification	#pts.
Failure	2	Failure	2
Good	0	Good	2
Very Good	0	Very Good	2

TABLE 8

OVERALL RESULTS IN PATIENTS INVOLVED IN LITIGATION					
Group I			Group II		
Classification	#pts.	%	Classification	#pts.	%
Failure	10	45.5	Failure	2	9.0
Good	10	45.5	Good	6	27.3
Very Good	2	9.0	Very Good	14	63.7
Total Good & VG		54.5	Total Good & VG		91.0

The worst results of the series were in patients involved in claims before the I.A.C. The two failures in group II were both in their late fifties, obese, had also suffered low back injuries and had severe degenerative disc disease in the lumbar as well as the cervical areas. Both also complained of headaches and therefore presented as almost total spinal axis pain.

DISCUSSION

Electrical stimulation was found to be 2 and one-half times as effective in achieving a good to very good result. In addition, the majority of results could be classed as very good (80% pain relief or better) compared to standard treatment where most of the satisfactory results could only be classed as good (50-80% pain relief).

The method of classification of pain relief is of course subjective but since there is no objective means of measuring pain relief, the method is felt to be valid. The criteria are strict enough to eliminate pain relief that is not significant.

Needle placement and electrical stimulation

This is a technique derived from traditional Chinese methods of acupuncture with the needles placed at traditional loci. The points used were:

- G.V. 14 — between the spinous processes of C7 and T1 — this area is innervated by the cutaneous branches of the dorsal rami of C6, C7 & T1.
- G.B. 20 — Inferior to the superior nuchal line, in a depression between the insertion of the sternomastoid muscle and the trapezius — this area is innervated by the greater and lesser occipital nerves and the third occipital nerve (dorsal ramus of C3).
- G.B. 21 — Midway between the spinous process of C7 and the acromion at the highest point of the shoulder.
- G.B. 36 — three inches lateral to the spinous process of T2.
- G.B. 37 — three inches lateral to the spinous process of T3.
- G.B. 38 — three inches lateral to the spinous process of T4.

The last four points are innervated by the cutaneous branches of the dorsal rami of C6 to D4. We also inserted needles in specific trigger points which were found by palpation and into any very tender areas that could be found.

The needles were stimulated by a battery pow-

ered direct current square wave generator with no negative phase with a pulse duration of 0.5 millisecond at 100 Hz and with a current just sufficient to be felt as a tingling sensation and not as pain. This current is of about one milliamp.

This threshold stimulation activates the large diameter (A-Beta) fibers of the sensory nerves which act to close a "gate" in the spinal cord inhibiting the passage of impulses through the small diameter (A-Delta and C) fibers. Gate-Control theory of Melzack and Wall (Science, 1965 vol-150 p.971).

There is a mechanism in the dorsal horns of the spinal cord that acts like a gate that can increase or decrease the flow of nerve impulses from peripheral fibers to the central nervous system. Somatic input is therefore subjected to the modulating influence of the gate before it evokes pain perception and response. The degree to which the gate increases or decreases sensory transmission is determined by the relative activity in large diameter (A beta) and smaller diameter (A delta and C) fibers and by descending influences from the brain. When the amount of information that passes through the gate exceeds a critical level, it activates the neural areas responsible for pain experience and response.

Hyperstimulation analgesia is one of the oldest known methods used for the control of pain. It is sometimes known as counter irritation and includes such methods as mustard plasters, ice packs, hot water bottles, cupping, etc. It is known that on occasion phantom limb pain can be relieved by injections of hypertonic saline into the stump. To explain this phenomenon, there must be a central biasing mechanism that inhibits transmission through the dorsal horns. High level stimulation such as the injection of saline could block self-exciting neuron loops and produce prolonged relief of pain.

The electrical stimulation may also relieve muscle spasm directly. Localized muscle spasm with accumulation of metabolites which produce pain and more muscle spasm in a vicious circle, I believe, is one of the main causes of pain in the cervical syndrome. Spasm may be initiated by relatively minor trauma to ligaments, discs, joint capsule or overstretching the muscles themselves. The condition can be self-perpetuating with a spasm-pain-spasm cycle. Interruption of the cycle at any point can be beneficial. This can be done directly by stimulation of the muscles themselves electrically, or, by blocking the pain through the gate control mechanism.

CONCLUSIONS

1. Significantly better results were obtained in patients treated with electrical stimulation of needles placed at specific points in the neck and thoracic region, than with standard treatment consisting of the use of a neck collar,

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Maine Blue Cross and Blue Shield News

MEDICAL ASSOCIATION BENEFIT PROGRAM EXPANDED

A great deal of interest has been shown, among both current and potential members of the Maine Medical Association Health Insurance Program, in catastrophic coverage.

The Health Insurance Committee of the Maine Medical Association decided to add \$500,000 Major Medical coverage to the program effective February 1, 1976. The catastrophic program has a \$500 calendar year deductible. After the deductible is satisfied, 80% reimbursement is provided up to \$30,000, and 100% after that to \$500,000. There is a \$30,000 limit for mental or nervous disorders.

Blue Alliance Mutual Insurance Company coverage was designed to supplement basic Blue Cross and Blue Shield, so a group must have both Blue Cross and Blue Shield before it can consider Blue Alliance Major Medical. When the Maine Medical Association Health Insurance Program was expanded to include catastrophic coverage, Blue Shield had to become a mandatory part of the program. Now, all members of the MMA program will have all those components: Blue Cross, Blue Shield, and \$500,000 Major Medical.

MAJOR MEDICAL BENEFITS

Benefits will be provided for reasonable and necessary charges for treatment of illness or accidental injury after the effective date of coverage. All services must be performed or prescribed by a physician.

Benefits include:

1. Services of a physician, except for routine physical examinations.
2. Charges made by a hospital for:
 - a. Board and room when all the benefit days provided under your Blue Cross certificate have been used.
 - b. Hospital services, other than board and room, furnished by the hospital, while you are an inpatient.
3. Use of operating room or treatment room.
4. Anesthetics and their administration.
5. X-ray services and diagnostic laboratory procedures.
6. Radiation therapy.
7. Oxygen and its administration.
8. Blood transfusions, including the cost of blood, blood plasma, and blood plasma expanders.
9. Drugs, medicines, and dressings used in the

hospital. Prescription drugs and prescription medications purchased for use outside of the hospital.

10. Services of a qualified professional physiotherapist.

11. Services of an R.N. in or out of the hospital and services of an L.P.N. in the hospital.

12. Rental of an iron lung or other durable equipment required for temporary therapeutic use.

13. Professional ambulance service for local transportation to or from the hospital but not for outpatient care for non-accidental illness.

14. Artificial limbs or other prosthetic appliances necessary for helping or correcting conditions from accidental injury or illness which occur after the effective date of coverage.

MAJOR MEDICAL EXCLUSIONS

Benefits will not be provided:

1. When the illness or injury is job-related or the result of war.
2. When care is received without cost because of federal, state, or local laws.
3. When care is provided in a veteran's facility.
4. Cosmetic or dental care except for the correction of defects caused by accidental injury.
5. For eyeglasses or hearing aids, or for examinations for the prescription or fitting thereof.
6. For care not related to treatment of illness or injury, or for services or supplies which are not covered medical expenses.
7. For pregnancy or its complications. Toxemia, convulsions, pernicious vomiting, or complications which require intraabdominal surgery are covered.
8. For travel, even if it is prescribed by a physician.
9. For convalescent, custodial, or sanatoria care.
10. When medical expenses are provided as benefits under a Blue Cross and Blue Shield Plan, or by a governmental plan or agency.

LIMITATIONS

Benefits are limited in these instances:

1. Covered expenses for treatment of nervous and mental conditions in the physician's office or outpatient department of a hospital will be paid on a 50% basis.
2. Benefits for treatment of nervous and mental conditions are limited to \$30,000 in a benefit period

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Chemotherapy of Tuberculosis

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ABSTRACT

Brief hospitalization, use of general medical facilities, outpatient therapy, and use of newer, more potent antituberculous agents are major innovations in the therapy of pulmonary tuberculosis. Isoniazid and ethambutol, used in combination, provide adequate therapy for all but the most severe cases of pulmonary tuberculosis. Isoniazid and rifampin, used in combination, provide cure rates approaching 100% in virtually all initially-treated cases with susceptible organisms. Retreatment cases can be successfully treated with a combination of rifampin and ethambutol. Short-term therapeutic regimens are currently being evaluated as alternatives to conventional 24-month therapy and may play a wider role in the near future. Intermittent therapy may be useful on an outpatient basis. Prophylaxis with isoniazid is an effective method of preventing breakdown of primary lesions, but each patient must be individually evaluated to weigh the risk of isoniazid toxicity against the risk of active disease.

Despite a continuing decrease in incidence in the United States, complete eradication of tuberculosis has been unsuccessful and large numbers of cases occur each year in high-risk populations. As experience in the diagnosis and therapy decreases, the application of existing knowledge to both case identification and therapy will become less efficient. The recent introduction of new antituberculous agents and new approaches to the therapy of tuberculosis complicates the problem. In addition, the treatment of tuberculosis has shifted, in part, to community hospitals and away from the tuberculosis sanatorium, so that hospital staff unfamiliar with the complex care of tuberculosis patients must now provide such care, often under the supervision of physicians without specialized training.¹

With these factors in mind, we undertook a review of the current therapy of tuberculosis in order to provide guidelines for the successful treatment of the tuberculosis patient.

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FACTORS INFLUENCING THE CHOICE OF ANTITUBERCULOSIS AGENTS

Factors influencing the choice of an antituberculous regimen may be grouped into two main categories: (1) the biologic properties of *Mycobacterium tuberculosis* and (2) the pharmacologic properties of the antituberculous agents.

Mycobacterium tuberculosis is an obligate aerobe which preferentially flourishes in those tissues with high oxygen tensions, e.g., the apices of the lung. It is characterized by its slow growth rate, ability to survive for long periods of time in a dormant state and relative resistance to antibiotics. In addition, the tubercle bacillus is able to develop in vivo drug resistance, often in a matter of weeks, when exposed to a single antituberculous agent. Its slow growth rate necessitates treatment of tuberculosis for long periods of time; the presence of dormant phases also necessitates long treatment so that all organisms will eventually be exposed to bacteriocidal drug levels when an active growth phase ensues.

The ability to develop drug resistance is the most important biologic characteristic of the acid-fast bacillus and the one which most influences our approach to chemotherapy. All natural populations of *Mycobacterium tuberculosis* contain varying numbers of drug-resistant organisms.² Fortunately, the occurrence of disease secondary to such organisms is rare, is limited to sporadic outbreaks, and has not appreciably increased in the past several years. The number of naturally-occurring, isoniazid-resistant organisms is about one in 100,000 bacilli, while the number of streptomycin-resistant organisms is about one in 1,000,000.³ Naturally-occurring resistance to other drugs is observed with similar frequency. The probability of resistance to both of the above drugs or to any combination of drugs is the product of the resistances. Since most tuberculous lesions contain a minimum of 100,000 organisms, a minimum of two antituberculous agents should be used in order to avoid the emergence of resistant organisms.⁴ It has been shown that administration of 1 gm/day of streptomycin for four months will cause 80% of patients to excrete acid-fast bacilli resistant to therapeutic doses and that 50% of those bacilli are resistant to streptomycin levels of 1000 μ g/ml.⁵

The pharmacologic properties of the antituberculous agents also play an important role in selecting a safe and efficient drug regimen. The ideal anti-

tuberculous agent should be: (a) nontoxic, (b) easily absorbed, (c) orally administered, (d) able to penetrate into all tissues and into tuberculous lesions, (e) active against both extra- and intracellular acid-fast bacilli at both acid and basic pH levels, and (f) able to destroy dormant as well as reproducing organisms. None of the drugs in use today meets all of these criteria, but the most commonly used anti-tuberculous agents closely approximate them.

ANTITUBERCULOUS REGIMENS

The physician today has many therapeutic options and his concern should be with the ease and lack of toxicity with which bacteriologic cure is achieved. Cure rates approaching 100% should be the accepted norm, and any case not rapidly responding to therapy must be carefully re-evaluated.

Until recently the mainstay of antituberculous therapy has been the combination of isoniazid (INH), streptomycin (STM) and para-aminosalicylic acid (PAS). Many other regimens have been advocated, but two offer distinct advantages.

Isoniazid and Ethambutol

As a result of low toxicity, ease of administration, patient acceptance, and excellent cure rates, most cases of pulmonary tuberculosis can be treated with a combination of isoniazid and ethambutol (EMB). INH is given in a single daily dose of 300 mg; EMB is given as a single daily dose of 25 mg/Kg for three months and then continued at 15 mg/Kg. The duration of treatment for both drugs is 24 months.

Extensive clinical investigation of this combination has been carried out by many investigators since the early 1960's. Bobrowitz and Robins⁶ compared INH and EMB to the combination of INH and PAS in patients with pulmonary tuberculosis of varying severity. Patients treated with INH and EMB received one of two regimens differing only in the dose of EMB. Regimen 1 contained EMB at 25 mg/Kg/day for 60 days, then 15 mg/Kg/day thereafter, while Regimen 2 utilized EMB at 15 mg/Kg/day from the outset. In Regimen 3 patients received 12 gm/day of PAS. In all regimens INH was administered at 300 mg/day. Sputum conversion was the endpoint of the study and was defined as three consecutive months of negative smears and cultures for acid-fast bacilli. After four months of therapy, 94.6% of patients on Regimen 1 had converted their sputum; in Regimen 2, 88.5% of the patients had sputum conversion. The patients receiving Regimen 3, which was the most commonly used double-therapy combination in the early 1960's, had an 82.3% sputum conversion rate. Drug toxicity was most frequent in the PAS treated group (33.7% compared to 7.8% for Regimen 1 and 10.5% for Regimen 2).

This study clearly demonstrated the efficacy of INH and initially-high dose EMB in the treatment of tuberculosis. However, the patient population in

this study group was mainly limited to those with minimal and moderately advanced disease.

A more complex study was reported in 1971 by Bobrowitz⁷ in which the efficacy of the following drug combinations was compared:

Regimen 1 — INH 300 mg/day
EMB 25/15 (25 mg/Kg/day for 90 days)
(15 mg/Kg/day thereafter)

Regimen 2 — INH 300 mg/day
PAS 12 gm/day
Streptomycin (1 gm/day for 90 days then 1 gm three times a week for 90 days)

Regimen 3 — INH 300 mg/day
PAS 12 gm/day
EMB 25/15

The patient population in this study was limited to cases of far-advanced cavitory tuberculosis, and after six months there was little difference between the three regimens in bacteriologic cure rates; all groups had conversion rates of approximately 85% to 90%. However, a significant difference in toxic manifestations and patient dropout was shown. Regimen 1 had a dropout rate of 15.1% compared to 41.9% in Regimen 2 and 32.4% in Regimen 3. Adverse drug reactions were almost exclusively secondary to PAS and STM, with an occasional reaction to INH and virtually no toxicity to EMB.

Approximately 5% of the patients in each group were removed from the study because of failure to respond to therapy. All of these cases had very far-advanced cavitory disease with bilateral cavitation and frequent giant cavities. In spite of the excellent results in patients with moderately advanced disease, the author concluded that further investigation was needed before INH/EMB could be recommended as the therapy for far-advanced cavitory pulmonary tuberculosis.

In 1974, Bobrowitz reported on the use of EMB 25/15 and INH 450 mg/day with or without the addition of streptomycin 1 gm/day for 90 days in the treatment of far-advanced cavitory tuberculosis.⁸ In view of the higher dose of INH, pyridoxine 50 mg/day was included in both regimens. At the end of six months no difference was found between the two groups in terms of sputum conversion, with sputum remaining positive in only 4.1% of patients receiving only INH and EMB, and in 5% of patients who were also receiving STM. The dropout rate due to drug toxicity suggested that EMB/INH was less toxic than EMB/INH/STM. A more rapid onset of sputum conversion occurred during the first month when streptomycin was added but thereafter the rates were the same.

The data suggest that EMB/INH 450 mg/day is adequate therapy for most cases of far-advanced cavitory tuberculosis; a small number of patients,

whose disease may be complicated by coincident medical illness, do not respond adequately to the two-drug combination.

INH and Rifampin

With the introduction of rifampin in the early 1960's, a major advance in antituberculous therapy was soon apparent. Used in combination with INH or EMB, or as part of a multi-drug regimen, cure rates approaching 100% were achieved with little drug toxicity in both initial and retreatment cases.

In the Public Health Service trials⁹ comparing rifampin/INH, rifampin/INH/EMB and INH/EMB/STM in the initial treatment of 631 patients with advanced cavitary tuberculosis, the following observations were made:

(1) The combination of rifampin/INH produced sputum conversion two weeks earlier than the INH/EMB/STM regimen, and the addition of EMB to the rifampin/INH regimen had no advantage in the patients studied.

(2) Ninety-five percent of patients had negative cultures by 16 weeks.

(3) Rifampin was well tolerated. Less than 2% of the patients had to discontinue the medication because of adverse drug reactions.

(4) Liver enzymes were often elevated in rifampin recipients, but only 5% of patients had transaminase levels above 100 units and there were no instances of clinical hepatitis which led to discontinuation of the drug.

The Public Health Service trial study concluded that rifampin/INH was the optimal initial treatment of tuberculosis available at that time and that, except for the high cost of rifampin, the regimen had no significant drawbacks.

Many other workers have confirmed the above data under a variety of clinical circumstances.^{10,11} Lees, et al¹⁰ reported on 88 patients initially treated with INH/rifampin and found a 92% sputum conversion rate after three months and a 100% sputum conversion rate after six months. Two patients developed generalized hypersensitivity reactions which necessitated the discontinuation of the rifampin. Other studies on the use of rifampin could be cited, but virtually all data show conversion rates approaching 100% within four to six months.

The efficacy of rifampin in the treatment of pulmonary tuberculosis is well established, but its exact role is still unclear.¹² Some authorities advocate its use in the initial treatment of tuberculosis, while others feel it should be reserved for treatment of cases failing to respond to initial therapy.

Those who advocate initial use point to the ability of rifampin to sterilize large tuberculous lesions and thus avoid the development of resistant infections. They state that the resulting high proportion of initial cures will largely eliminate the problem of complex retreatment cases.

On the other hand, it is argued that the initial use of rifampin will only contribute to increasing rifam-

pin resistance and to the elimination of the most potent agent used in the retreatment of tuberculosis. Authorities against initial use suggest the establishment of two separate regimens, one including INH that is used for initial therapy, and another containing rifampin that is used only for retreatment. Use of a rifampin regimen solely in retreatment, they argue, will still give a 95% sputum conversion rate for those patients initially treated with an INH regimen who fail to achieve bacteriologic cure. It is not yet clear which approach is correct, or if indeed there has to be rigid adherence to a single formula.

We feel at this time that the routine initial treatment of minimal and moderate pulmonary tuberculosis can be carried out with INH/EMB. However, in patients with far-advanced cavitary disease, INH/rifampin should be used. Other drug combinations do not offer any advantage over either of these regimens in initial therapy and their use is not recommended.

It is currently recommended that all patients receiving conventional antituberculous therapy be treated for a minimum of 18 to 24 months, depending on the severity of the disease and the rapidity of sputum and x-ray clearing. After two years of chemotherapy, relapse rates are extremely low (less than 2%). Outpatient follow-up need not continue, but patients should be advised to contact their physician for any new chest symptoms or constitutional problems.¹³ Continuing chemotherapy for more than 24 months following successful initial therapy is not necessary.

SHORT-TERM THERAPY

With the introduction of rifampin and recognition of its unique antituberculous properties, there has been renewed interest in short-term therapy of pulmonary tuberculosis. Reduction in the total duration of therapy to one year or less without an accompanying decrease in cure rates would be of enormous value, especially in countries where financial or social conditions make 18 to 24 month therapy difficult. The advantages of short-term therapy are (1) a decrease in drug toxicity due to decreased drug exposure, (2) increased patient compliance, and (3) decreased need for extensive follow-up facilities.

Prior attempts at short-term therapy have been unsuccessful because of unacceptably high relapse rates, but recent work reported by Fox and Mitchison¹⁴ suggests that with multiple drug regimens or with the use of INH/rifampin, the relapse problem is minimized. They report that a combination of INH, STM and rifampin daily for six months yielded virtually 100% sputum conversion; only two out of 112 patients had relapses, both of which occurred within 18 months after discontinuation of the therapy. The relapse patients were retreated and followed for a total of thirty months after the cessation of therapy and no further relapses were noted.

A repeat study using the same regimen in 152 patients showed a comparable rate of relapse. All patients studied had moderately to far-advanced tuberculosis.

Further studies assessed the use of INH/rifampin (without streptomycin) for six months. This was particularly important, as the elimination of an injectable drug increased patient acceptance and made self-administration of medications feasible. The results were ambiguous. Only one patient failed to convert his sputum after six months of therapy, but after 12 months of follow-up there was a 5% (9/170) relapse rate, a figure which, if confirmed by larger studies, would be higher than one would accept after standard two-year therapy. INH and rifampin, while successfully converting sputum to negative within six months, does not appear to be satisfactory unless given for longer periods.

Other studies indicate that six to 12 months of therapy with the addition of ethambutol to INH and rifampin will result in an extremely low relapse rate. While these preliminary data suggest that short-term therapy for pulmonary tuberculosis is feasible, we feel it is presently suited only for situations in which conventional 18 to 24 month therapy cannot be carried out. Further investigation may, however, allow us to significantly reduce the duration of treatment in the near future.

INTERMITTENT THERAPY

For patients who cannot be relied upon to take daily medications, but who can be followed as outpatients in a clinic or at home two times a week, intermittent therapy should be considered as a substitute for long-term hospitalization. INH 15 mg/Kg with either STM 25-30 mg/Kg or EMB 50 mg/Kg, given twice weekly, have been shown to produce acceptable cure rates. When INH is used in this type of regimen, pyridoxine 50 mg/day should be given with each dose to prevent peripheral neuritis. Optic neuritis has not been a problem with the increased dose of ethambutol, and reactions to STM are of the same type and frequency as those usually encountered. Such therapy is not currently recommended as a substitute for daily therapy by the American Thoracic Society and should only be given after an initial period of daily therapy for two to six months, depending on the extent of the disease; it should be continued for a total of 24 months. Acquired drug resistance is not a problem as long as a regular treatment schedule is followed.^{15,16}

It would appear from the results of daily therapy with rifampin that it would be the ideal agent for intermittent therapy; however, this has not been proven. Biweekly use of rifampin has been associated with an adverse reaction rate as high as 20%, usually after six months of therapy.¹⁷⁻¹⁹ These reactions fall into two categories. The most common is a systemic reaction, probably induced by the deposition of immune complexes in small blood vessels

and producing fever, joint pain and abdominal and muscle cramps. The other is an antibody-induced thrombocytopenia. These reactions have also been described after the reinstitution of rifampin as long as several months after therapy has been discontinued.

In contrast to the above experience, the use of once-weekly rifampin at 30 mg/Kg has, in one study, been shown to be extremely potent in producing sputum conversion when combined with EMB 100 mg/Kg or INH 15 mg/Kg, and not to be associated with any severe side effects.²⁰ The authors postulated that since the total duration of the intermittent therapy was less than six months (at that time, patients were switched to another regimen), the immunologic sensitization never developed.

It is our feeling that rifampin should not be used on an intermittent basis until more information is available about its immunologic effects.

RETREATMENT

Retreatment cases are among the most difficult problems in the therapy of tuberculosis. Widespread lung destruction as sequelae of previous infections and multiple drug toxicities and drug resistances may be present. Cure rates in the past have been low, and the use of more toxic multiple drug regimens that rely on less efficient second line drugs has been necessary. The use of rifampin in combination with ethambutol appears to have markedly changed those statistics.²¹ These two drugs have provided cure rates above 95% in retreatment cases, as demonstrated by numerous studies. As a result of the excellent cure rates with currently available initial and retreatment drug regimens, patients with persistently positive sputum will be rarely encountered.

DRUG TOXICITY

Isoniazid

As INH is the most widely used antituberculous agent, its toxicity is perhaps the most frequently encountered and therefore its toxic manifestations should be well understood.²²

The most important toxicity of isoniazid is its effect upon hepatocellular function. From 10% to 20% of patients taking 300 mg of INH daily will show some transient or prolonged rise in SGOT and SGPT and a pathological picture resembling a mild viral hepatitis.^{23,24} This change in liver function is usually benign, with enzymes returning to normal values or stabilizing after several months and with the patient showing no clinical signs of hepatitis. A more serious, idiosyncratic type of progressive hepatocellular damage occurs rarely. It is virtually unheard of below 20 years of age, and its frequency increases from approximately 0.3% in the age range of 20-34 to 2.3% at age 50 and above. Occasional cases of massive liver atrophy with death have been reported and, although other contributing factors (i.e. alcohol or prior liver damage) may have been

present in the initial reports, INH appears to be directly implicated.²⁵ Consideration of the above data is of extreme importance in the prophylaxis of tuberculosis with INH, but the benefits of INH as a therapeutic agent in active tuberculosis make its possible hepatic side effects of less concern in treating active disease.

The most common side effect of isoniazid is peripheral neuropathy. This is infrequent with dosage of 300 mg daily and routine use of pyridoxine is not recommended unless pre-existing neuropathy is present. Other potentially severe side effects and idiosyncratic reactions are:

- (1) central nervous system stimulation or depression, sometimes resulting in overt psychosis,
- (2) induction of lupus erythematosus or rheumatoid-like syndromes,
- (3) hematologic disturbances, including hemolytic anemic, pyridoxine responsive anemia, agranulocytosis, and red cell aplasia,
- (4) hypersensitivity reactions consisting of fever, rash, eosinophilia, and arthralgias.

Some of these reactions may be self-limited, while others may be progressive and require discontinuing INH and/or desensitization procedures.

Ethambutol

This agent, now frequently used in combination with INH in initial therapy of pulmonary tuberculosis, has one major serious side effect: optic neuritis. The neuritis is dose related and may manifest itself by loss in visual activity or color discrimination. At currently employed dosages of either 15 mg/Kg/day or 25 mg/Kg/day, the neuritis has rarely been described; it was primarily observed at doses of 50 mg/Kg/day. In the Public Health Service trials using ethambutol at 15 mg/Kg/day, there was no significant difference noted in the frequency of decreased visual acuity in the patients taking EMB, as compared to patients on other drug regimens. It is currently recommended that patients taking ethambutol have monthly monitoring of visual acuity and color discrimination, and that any significant change from baseline levels be evaluated fully.^{26,27}

Rifampin

The daily use of rifampin is associated with an occasional elevation of liver enzymes and bilirubin values; this is partially caused by false elevations due to interference of rifampin with bilirubin assay techniques. There are isolated occurrences of clinical hepatitis and, in addition, rare cases of generalized hypersensitivity reactions have been reported. In the Public Health Service cooperative trial using 600 mg/day of rifampin, approximately a 1% reaction rate was noted. Other studies have reported reaction rates in the 3% to 5% range, with the incidence of asymptomatic rises in transaminase as high as 18%. Rifampin is felt by most authors to

be a reasonably benign drug, although the combination of rifampin/INH appears slightly more likely to induce hepatocellular damage than rifampin/EMB.⁹

An additional, recently-described side effect of rifampin is its interaction with oral contraceptives; contraceptive activity is diminished by increased estrogen metabolism.²⁸

Streptomycin

In addition to its pharmacological side effects, a major disadvantage of STM is that it must be given parenterally. This requires the need for medical personnel to administer the drug and increases patient nonacceptance.

The treatment-limiting toxicity of streptomycin is its effect on the vestibular branch of the eighth cranial nerve. Lesser effects on the auditory branch can sometimes be seen, but vestibular dysfunction usually precedes any decrease in hearing. Renal insufficiency can also be observed, but it is less common than with the other injectable aminoglycosides, kanamycin, capreomycin and viomycin. Elderly patients are especially sensitive to the vestibular damage caused by streptomycin, and lower doses are often necessary to prevent the rapid onset of toxicity. Monthly audiograms should be done on all patients receiving injectable aminoglycosides, and renal function should be carefully monitored, especially in patients with pre-existing renal damage. Because of the high percentage (up to 25%) of patients who demonstrate vestibular damage after long courses of streptomycin, the total dose should be limited to 1 gm/day for 90 days, and then 1 gm three times a week for an additional sixty days.

SECOND-LINE DRUGS

Four other oral antituberculous agents are currently employed in the United States, but all are considered second-line drugs whose usefulness is limited by their toxicity and lack of demonstrated superiority over less toxic agents. These drugs are para-aminosalicylic acid (PAS), pyrazinamide, cycloserine, and ethionamide. In addition, kanamycin, viomycin and capreomycin, all of which are given only by injection, are rarely used in tuberculosis therapy because of their toxicities and their marginal effectiveness.

The dosage, route of administration, major adverse effects, and procedures for monitoring for adverse effects of first and second-line antituberculous drugs are presented in Tables 1 and 2, respectively.

HOSPITALIZATION OF TUBERCULOSIS PATIENTS

Routine long-term hospitalization of all tuberculosis patients is no longer necessary in view of the increased efficacy of modern chemotherapy.^{29,30} Current recommendations as to the length of hospitalization or criteria for discharge of tuberculosis patients are not standardized, and wide variations in clinical practice occur. We feel that in most cases

TABLE 1
FIRST-LINE DRUGS IN THE THERAPY OF TUBERCULOSIS

<i>Drug</i>	<i>Daily Dose</i>	<i>Route of Administration</i>	<i>Major Adverse Effects</i>	<i>Monitoring</i>
Isoniazid	300 mg (single dose)	Oral	Hepatitis Peripheral neuritis CNS disturbances Hematologic and rheumatoid disorders	Serum transaminase
Rifampin	600 mg (single dose)	Oral	Hepatitis Thrombocytopenia (with intermittent use)	Monthly serum transaminase
Ethambutol	25 mg/Kg for 90 days then 15 mg/Kg (single doses)	Oral	Optic neuritis	Monthly visual acuity and color tests
Streptomycin	15 mg/Kg up to 1.0 gm daily for 90 days, then 1.0 gm three times weekly (single doses)	Intramuscular	Vestibular toxicity Auditory toxicity Renal insufficiency	Monthly blood urea nitrogen and audiogram

TABLE 2
SECOND-LINE DRUGS IN THE THERAPY OF TUBERCULOSIS

<i>Drug</i>	<i>Daily Dose</i>	<i>Route of Administration</i>	<i>Major Adverse Effects</i>	<i>Monitoring</i>
Para-amino-salicylic acid	200 mg/Kg up to 12 gm (three divided doses)	Oral	Gastrointestinal disturbances Hepatitis Lupus-like syndrome	Monthly serum transaminase
Pyrazinamide	40-50 mg/Kg up to 2-3 gm (three divided doses)	Oral	Hepatitis Hyperuricemia	Monthly serum transaminase and uric acid
Cycloserine	15 mg/Kg up to 1.0 gm (four divided doses)	Oral	CNS disorders (seizures, psychosis)	Evaluation of neurological status
Ethionamide	10-15 mg/Kg up to 1.0 gm (four divided doses)	Oral	Hepatitis Gastrointestinal upset	Monthly serum transaminase
Kanamycin	15 mg/Kg up to 1.0 gm five times weekly	Intramuscular	Renal insufficiency Auditory toxicity Vestibular toxicity	Same as for Streptomycin
Viomycin	15 mg/Kg up to 1.0 gm five times weekly, or 2.0 gm two times weekly	Intramuscular	Auditory toxicity Vestibular toxicity Renal insufficiency	Same as for Streptomycin
Capreomycin	15 mg/Kg up to 1.0 gm five times weekly	Intramuscular	Auditory toxicity Vestibular toxicity Renal insufficiency	Same as for Streptomycin

in which minimally to moderately advanced disease is present, brief hospitalization is sufficient for patient education and for observation for possible hypersensitivity or idiosyncratic drug reactions. More complex cases may require hospitalization for longer periods, but even far-advanced cases can often be discharged in a matter of weeks.

The traditional criteria of awaiting three negative smears and cultures before discharge was based on the impression that as long as acid-fast bacilli could be seen in the sputum or grown in culture medium, the patient was infectious. The limited infectivity of patients taking antituberculosis agents has been suspected for many years, and it has been shown that most cases of spread of tuberculosis occur from undiagnosed cases, not from patients undergoing active chemotherapy.^{31,32}

Several recent studies suggest that after three to four weeks of antituberculous therapy, most of the acid-fast bacilli excreted are of low viability and consequently unlikely to cause infection in contacts. Examination of PPD (purified protein deriva-

tive of tuberculin diagnostic agent) conversion rates among household contacts of patients discharged with positive smears while on adequate chemotherapy has revealed an extremely low incidence of conversion.³³ Furthermore, continued clinical improvement, sputum conversion and x-ray improvement have been observed in patients discharged from the hospital after three to four weeks of therapy, provided a good outpatient program is initiated.³⁴ Early discharge of patients with positive sputa must always be considered in relation to the socio-economic nature of tuberculosis, and patients who are felt to be unreliable because of drug or alcohol abuse or because of character disorders must be hospitalized for longer periods of time. Consideration should be given to alternate forms of therapy, e.g., short-term, intermittent, or supervised drug administration, but above all it should be emphasized that the best chance of cure for any patient lies in the initial course of therapy. Every effort must be made to achieve bacteriologic cure the first time the patient is treated.

CHEMOPROPHYLAXIS OF PULMONARY TUBERCULOSIS

Chemoprophylaxis of pulmonary tuberculosis is based on the demonstration that skin test conversion is caused by initial infection with *Mycobacterium tuberculosis* and that failure to treat the primary infection results in the appearance of active disease in a number of those infected.^{35,36} Not all people with a positive skin test are equally at risk for the development of active disease, and the individual circumstances must always be evaluated so the risk of breakdown can be weighed against the possibility of serious drug reaction. For practical purposes, we must concern ourselves with the specific use of isoniazid as a chemoprophylactic agent and must examine in detail the possible hepatocellular damage resulting from its use.

The discovery of a positive skin test necessitates placing the patient into the correct risk category so that factors for and against chemotherapy can be evaluated. Generally, either a high, moderate or low risk is assigned.

High Risk

Household contacts. The high-risk group includes all household contacts of patients with active tuberculosis. All such contacts should be screened with an intermediate PPD and with chest x-rays. It is estimated that approximately one in thirty household contacts will develop active tuberculosis if not treated. Any household contact with an abnormal chest x-ray should be fully evaluated for the presence of active tuberculosis, regardless of the status of his skin test. If a rapid determination of activity cannot be made, it is suggested that such patients be started on INH and EMB until the evaluation can be completed, and either continuation of therapy for active disease or chemoprophylaxis with INH alone is decided upon.

In the adult population, if a negative chest x-ray occurs together with a positive intermediate PPD, it is recommended that 300 mg of INH be given daily for one year. If a negative intermediate PPD coexists with a negative chest x-ray, no immediate therapy is necessary. If exposure was minimal, it is recommended that the skin test be repeated in three months and therapy initiated at that time if conversion has taken place. If the initial exposure was very heavy, chemoprophylaxis should be started and continued for three months, at which time the skin test should be repeated. If the skin test is still negative, INH prophylaxis can be discontinued, but if conversion has taken place, INH should be continued for a total of 12 months.

In the pediatric age group, it is recommended that all household contacts below the age of six who have a positive skin test be treated with INH 10-20 mg/Kg up to 300 mg for one year. There are two possible approaches to the child who has a negative skin test and a history of household exposure. Certain authorities suggest that they should be treated for three months and the skin test repeated. If it remains

negative, INH can be terminated; if conversion has taken place, treatment should be continued for one year. Other authorities advocate a mandatory one year of INH prophylaxis for pediatric household contacts regardless of skin test status. This is because of their increased risk of developing active tuberculosis and the almost nonexistent incidence of adverse effects of INH among children.³⁷

Recent converters. Also at high risk are those patients with a known recent conversion of their skin tests within the prior 12 to 24 months. The risk of developing active disease is greatest (approximately 3%) in the first year of the conversion, and decreases each year thereafter. Establishment of the exact time of conversion is of extreme importance to facilitate assignment to the correct risk category.

These patients should be screened with chest x-rays and, if no abnormality is found, prophylaxis with 300 mg INH a day for one year should be undertaken. Since there are great variations among reading procedures and techniques of administration of skin tests, rigid criteria for "conversion" must be adhered to. They should include an increase in induration of at least 6 mm, from a total of less than 10 mm to a total of greater than 10 mm, and must also include consideration of any so-called "booster effect." This effect is seen most frequently in patients over 50 years of age and occurs when delayed hypersensitivity wanes, so that the first of two tuberculin skin tests may serve to "boost" the response to a second test given within a year or two. This may give rise to a false conversion when in fact the tests have been positive for many years.

Inadequately treated tuberculosis. In the remaining high-risk group, we find patients with a definite past history of active tuberculosis who have never received adequate chemotherapy, and patients with positive skin tests who have radiologic evidence of inactive tuberculosis. The incidence of developing active disease in these patients is about 1 in 75 per year. These patients often are from the pre-antibiotic era and may have been treated with thoracoplasty or pneumothorax therapy or may have received STM and/or PAS, but never INH. It is recommended that these patients receive one year of INH 300 mg/day, with due consideration that this group of patients is often elderly and at higher risk for INH-induced hepatitis. Close follow-up is required and possible signs of INH toxicity must be carefully evaluated.

Moderate Risk

Patients found to have positive skin tests and normal chest x-rays, with no history of recent household contact and no evidence of recent conversion, are at moderate risk of developing active tuberculosis if they fall into several special clinical categories as outlined below. It is recommended by the American Thoracic Society that they receive one year of prophylaxis; life-long continuation of INH does not confer any added advantage.³⁶

Patients on corticosteroids or immunosuppressive agents. The exact incidence of breakdown of inactive tuberculous lesions in patients receiving immunosuppressive drugs is not known, but there is sufficient clinical evidence to implicate these agents in the development of active disease if a previously inactive focus is present. It is currently recommended that patients in this category receive one year of INH prophylaxis. Intermittent INH "coverage" of these patients while on immunosuppressive or corticosteroids is to be avoided, as it might foster the emergence of resistant organisms.

The presence of hematologic or reticuloendothelial diseases. It is difficult to separate these patients from the above groups, as they are often treated with immunosuppressive agents. They should be treated with one year of INH at the beginning of their disease process or upon institution of therapy. Accurate data regarding the past skin test status of such patients is essential so that current skin tests may be properly interpreted in view of the anergy these patients may exhibit. In all cases when such data are not reliable, the possibility of active tuberculosis must be exhaustively pursued.

The presence of diabetes mellitus. The breakdown rate of primary lesions in patients with diabetes mellitus appears to be higher than in non-diabetic patients. Presentation of active tuberculosis may be atypical or modified by the diabetes and active disease must be excluded. If no indication of activity is present, these patients should receive one year of INH prophylaxis.

Silicosis. Patients with proven or suspected pulmonary silicosis should be given INH prophylaxis. The silicotic host is more susceptible to dissemination of tuberculosis, and the widespread parenchymal destruction often present makes any degree of active tuberculosis more of a threat.

Post Gastrectomy. For reasons which remain unclear, possibly related to nutritional status of some non-specific decrease in host resistance, patients with subtotal or total gastrectomy have a high incidence of breakdown of their primary lesions. INH prophylaxis is recommended for patients with a gastrectomy who are found to have a positive skin test and a normal chest roentgenogram.

Low Risk

The last group of people to be considered for INH prophylaxis are those in the low-risk category where the incidence of developing active tuberculosis is about 1 in 1400 per year. These are people with a normal chest roentgenogram and a positive skin test of unknown duration who do not have any other indication for chemoprophylaxis. Under these circumstances, each case should be individualized, but prophylaxis is not indicated for patients above 35, at which time the risk of INH-associated hepatitis exceeds 1% and is therefore greater than the risk of breakdown.

FOLLOW-UP OF PATIENTS WITH INH PROPHYLAXIS

All patients placed on INH must have careful and frequent medical evaluation for the presence of INH-induced hepatocellular damage. There is no current agreement on the best method of monitoring these patients, or on the significance of the presence of mild elevations in transaminase, but certain precautions would seem indicated. All patients should be initially screened for the presence of liver dysfunction before prophylaxis is begun. While mild or moderate chronic liver disease is not an absolute contraindication to the use of INH, patients with such damage have less reserve if INH toxicity should occur. Individuals who develop clinical hepatitis while on INH should have the medication discontinued. All patients with a continued significant elevation in transaminase (above 100 units) must be carefully monitored and if the rise continues to above 250 units, the INH should be discontinued. The presence of a mild rise in transaminase (between 100 and 250 units) as well as abnormality in another liver function test, e.g., alkaline phosphatase, requires discontinuation of the drug.

CORTICOSTEROIDS

While not indicated in the routine treatment of pulmonary tuberculosis, corticosteroids have limited application in the therapy of severely toxic patients. They must never be given unless adequate antituberculous coverage is provided, and the occurrence of steroid-induced side effects must be evaluated in each individual case.

The benefits of corticosteroid therapy in the treatment of pulmonary tuberculosis are limited to the first one to three months during which a more rapid clinical improvement may occur. This is manifested by loss of fever, weight gain, and an increased feeling of well being. Long-term studies demonstrate, however, that at the end of six to twelve months of chemotherapy there is an equal degree of clinical improvement in patients treated with and without steroids.

Clinical or radiographic worsening after steroid withdrawal, and rapid progression of tuberculous lesions while on steroids has been reported, so careful monitoring of these patients is mandatory. The currently recommended dose of corticosteroids is the equivalent of 40 mg/day of prednisone to be given for a maximum of six weeks and tapered gradually to avoid any rebound phenomena.

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- Dr. Steele, 472 Main St., Lewiston, Maine 04240.
Dr. Clapp, 215 College St., Lewiston, Maine 04240

THE "CERVICAL SYNDROME" — *Continued from Page 68*

1. traction, analgesics, muscle relaxants, etc.
2. The degree of improvement as regards pain reduction and reduction of stiffness was greater with electrical stimulation.
3. The duration of disability was much shorter.
4. The time of treatment was greatly reduced.
5. The presence of D.D.D. or associated litigation did not significantly affect the results in group II.
6. Patients suffering from the cervical syndrome were found to have a much higher incidence of degenerative disc disease on x-ray compared to asymptomatic patients suggesting that cervical spondylolysis predisposes to the development of pain in and stiffness of the neck.
7. I would consider electrical stimulation as the treatment of choice for cervical syndrome.

416 Sabattus St., Lewiston, Maine 04240

SPECIAL REPORT

Date Opinion Filed
January 19, 1976

Reporter of Decisions
Docket No. 1267
Law Docket No. Ken-75-6

Supreme Judicial Court of Maine ABDOLLAH GASHGAI, M.D.

v.

MAINE MEDICAL ASSOCIATION, ET AL

WERNICK, J.

This is an appeal by the defendants, Maine Medical Association (a Maine corporation), the Ethics and Discipline Committee of the Maine Medical Association and Bruce Trembly, M.D., in his capacity as Chairman of said Committee, from a (Kennebec County) Superior Court judgment embodying a permanent injunction against defendants.

The judgment was entered in a civil action against defendants instituted on May 10, 1974 by plaintiff, Abdollah Gashgai, M.D., a medical doctor duly licensed to practice medicine in the State of Maine and a member of the defendant Maine Medical Association. The complaint alleged, inter alia, that the Ethics and Discipline Committee of the Maine Medical Association, over the signature of its Chairman, Dr. Trembly, had issued a report concerning plaintiff and distributed it to

"a variety of individuals, institutions, bureaus and offices, in violation of the by-laws and procedures of Defendant Association."

The complaint also averred that the conclusions of the report

"... are so tainted by... failure to accord due process that they have no basis in law or fact", and the actions of the Committee and its Chairman

"... are so arbitrary, capricious, discriminatory, willful, wanton and reckless as to cause irreparable loss and damage to Plaintiff."

Asserting that he would

"... suffer immediate and irreparable injury, ... unless said report ceases to be circulated and unless all existing copies are retrieved",

plaintiff sought preliminary and permanent injunction prohibiting "... further circulation of said report" and commanding the parties who had sent or delivered the report to other persons "to retrieve all copies" sent or delivered.

After defendants had answered the complaint, the Justice presiding in the Superior Court held a hearing on June 12, 1974. On September 12, 1974, he filed findings of fact all of which are adequately supported by evidence and are, therefore, here controlling. These findings disclose the following factual situation.

On March 8, 1974 Mrs. Rayna B. Leibowitz, acting in her official capacity as a Medical Claims

Consultant for the Department of Health and Welfare of the State of Maine, and in accordance with instructions given her by Dr. George Sullivan acting in his capacity as a consultant to said Department and a member of the Board of Registration in Medicine of the State of Maine, forwarded to defendant Trembly, by letter, a request on behalf of the Department for an investigation by the Maine Medical Association Ethics and Discipline Committee of certain aspects of Dr. Gashgai's medical practice and conduct in specific instances. On March 25, 1974 Mrs. Leibowitz sent another letter providing supplemental information and renewing the Department's request for investigatory assistance.

Shortly after March 8, 1974 Dr. Trembly, by telephone, and without indicating that charges had been lodged against Dr. Gashgai, requested that he appear on March 27, 1974 before a committee of the Maine Medical Association. At that time, Dr. Trembly did not further identify the committee. Subsequently, an undated letter was sent to Dr. Gashgai confirming the date and time of the meeting and informing Dr. Gashgai that a committee of the Maine Medical Association (still not more specifically identified) had been asked to look into the reasons for particular charges Dr. Gashgai had made to the Department of Health and Welfare.

At all times here relevant Dr. Gashgai has been a member of the Maine Medical Association which (although a corporation) is, basically, a voluntary association of individuals licensed to practice medicine in the State of Maine. A condition precedent to membership in the Maine Medical Association is membership in a County Medical Society which is a component of the Maine Medical Association. Dr. Gashgai is a member of the Kennebec County Medical Society, one such county component.

Dr. Gashgai honored the request of Dr. Trembly and appeared on the evening of March 27, 1974 at the Holiday Inn in Augusta where he met informally with Dr. Trembly and other doctors who were members of the Ethics and Discipline Committee of the Maine Medical Association. It soon became apparent to Dr. Gashgai that the meeting had lost its original "conversational" tone and had become accusatory of him. It then dawned on Dr. Gashgai that Dr. Trembly and the others were actively en-

gaged in investigating charges against him which were serious.

During a questioning of Dr. Gashgai lasting approximately two hours Dr. Trembly and the others on the Committee made references to invoices and other documents which had been provided to them by the Department of Health and Welfare. They also utilized information contained in confidential documents supplied to the Committee, without Dr. Gashgai's prior knowledge or consent, by Dr. Henry J. Wheeler, Medical Director of the Augusta General Hospital. These same documents ultimately formed the basis of the conclusions reached by the Committee.

On March 27, 1974, without having undertaken any investigation additional to that constituted by the questioning of Dr. Gashgai on that date, the Committee issued a report containing the conclusions that the invoices submitted by Dr. Gashgai to the State Department of Health and Welfare showed gross overutilization, malpractice and unethical practice by Dr. Gashgai. The report also recommended that Dr. Gashgai be severely reprimanded.

The Committee sent the report to Dr. Gashgai and also to the Maine Medical Association, the Board of Registration in Medicine of the State of Maine, the Department of Health and Welfare of the State of Maine and the Medical Director of the Augusta General Hospital. As the result of having received the report, the Department of Health and Welfare placed Dr. Gashgai on a "constant surveillance" list, thereby requiring that all invoices henceforth submitted by Dr. Gashgai be carefully reviewed to evaluate the propriety of his charges.

The presiding Justice supported the permanent injunction issued by him¹ with the following conclusions: (1) the activities of Dr. Trembly and the other persons who had acted with him as members of the Committee on Ethics and Discipline of the Maine Medical Association were in violation of various of the Association's by-laws; (2) said activities contravened procedural due process requirements of the Constitutions of the United States and the State of Maine as applicable by virtue of the special relationship here existing between a governmental agency of the State of Maine and the Maine Medical Association and its Committee — a relationship sufficient to transform the Committee's activities into governmental action subject to constitutional due process mandates.

Defendants maintain on appeal that the findings of the presiding Justice of violations of the Association's by-laws and his references to the legal consequences flowing therefrom were not intended to be independently separate grounds of decision but were offered only as ancillary support for his constitutional due process conclusions. Defendants contend, therefore, that the only issue to be decided in this appeal is the correctness of the presiding Justice's holding that defendants' actions here in

question are subject to the due process mandates of the United States and Maine Constitutions.

We disagree with defendants. Our study of the record convinces us that plaintiff had maintained before the presiding Justice that the violations of the Association's by-laws were discreet grounds entitling him to the injunctive relief sought by him independently of his additional claim of constitutional due process violations. The presiding Justice addressed each of these separate claims and concluded that each was a sufficient, independent ground justifying the injunctive relief he ordered.

We agree with the presiding Justice that the Committee actions of which Dr. Gashgai complains were in violation of particular by-laws of the Maine Medical Association and involved actual, and imminently threatened, injury to Dr. Gashgai — injury which was irreparable because it tended to impair Dr. Gashgai's opportunity to earn a livelihood through the practice of his chosen profession and, therefore, required the injunctive relief ordered. We sustain the judgment of the Superior Court Justice on this ground and do not reach the constitutional due process question.

The presiding Justice found that the Ethics and Discipline Committee of the Maine Medical Association had violated the Association's by-laws in three critical respects.² The presiding Justice then reached the conclusion of law that said

"actions . . . were a nullity under the Defendant Maine Medical Association's own internal rules."

The presiding Justice's findings as to the factual occurrences held to be violations of by-laws were adequately supported by evidence and are, therefore, here conclusive. The Justice's interpretation of the meaning of the by-laws, as applicable to the factual occurrences, was correct. Also correct was the presiding Justice's conclusion of law regarding the nullity of defendants' actions as a basis for judicial intervention to grant the injunctive relief here ordered.

Courts have relied on various rationales to justify their intervention to control the activities of private associations.³

For present purposes, since the by-laws of the Maine Medical Association here taken to be applicable are consonant with statutory and constitutional mandates and violate no general public policy of this State, they provide a proper basis for application of the "contract" rationale traditionally relied upon to justify judicial intervention to control the activities of private corporations. This Court recently utilized this "contract" approach in *Libby v. Perry*, Me., 311 A.2d 527 (1973), holding that the by-laws of a private association

"provided they are not unreasonable, nor contrary to public policy nor to constitutional or statutory requirements, . . . [are] a valid enforceable contract between the members and the association . . . [which] govern their mu-

tual rights and liabilities." (p. 532)

Thus, insofar as they here imposed obligations and restrictions upon the Association, the Association's by-laws are contractual terms cognizable, and enforceable, by a Court in accordance with the principles of contract law.

It is not material that the Department of Health and Welfare may have requested the Ethics and Discipline Committee to investigate particular facets of Dr. Gashgai's medical practice and conduct without knowledge of, or relation to, whether Dr. Gashgai was a member of the Maine Medical Association. The crucial point is that Dr. Gashgai was in fact a member of that Association. As such member, and specifically in reference to an investigation of his activities in the conduct of the practice of medicine undertaken by one of the standing committees of the Maine Medical Association in ostensible furtherance of purposes for which the Association exists, Dr. Gashgai was entitled to the protections afforded by the by-laws of the Association as the terms of a contract between the Association and him. Violations of the by-laws in the Association's dealings with Dr. Gashgai are thus breaches of contract specifically relating to Dr. Gashgai which he is legally entitled to remedy by resort to the Courts.

It was not here requisite, as a pre-condition of obtaining judicial relief, that Dr. Gashgai exhaust remedies open to him within the Maine Medical Association.

This principle of exhaustion of internal remedies, as generally followed in cases in which Courts are asked to assert control over private associations is, like the doctrine of "exhaustion of administrative remedies" to which it bears a degree of kinship,⁴ a principle of policy rather than a limitation of the Court's jurisdiction of the subject matter. Cf. *State of Maine ex rel. Attorney General and the Board of Environmental Protection v. R. D. Realty Corporation, Me.*, ___ A.2d ___ (1975).

As policy, the "exhaustion" requirement has been subject to a long and firmly established exception rendering it inapplicable in situations in which the Court may readily discern a plain, and not insignificant, violation of the private association's constitution or by-laws. The conceptual rationale behind this exception is that when a Court confronts a plain and substantial violation of the constitution or by-laws of a private association, the Court has been provided with the private association's own antecedent stamp of the nullity of the actions in question as violative of the basic principles by which the association is governed. *California State University, Hayward v. National Collegiate Athletic Association*, 47 Cal. App. 3d 533, 121 Cal. Rptr. 85 (1975); *Niner v. Hanson*, 217 Md. 298, 142 A.2d 798 (1958); *Jenkins v. Local Union No. 6313*, ___ Mo. ___, 271 S.W.2d 71 (1954); *Morris v. Peters*, 203 Ga. 350, 46 S.E.2d 729 (1948); *Smetherham v. Laundry Workers' Union*, 44 Cal. App. 2d 131, 111

P. 2d 948 (1941); *Abdon v. Wallace*, 95 Ind. App. 604, 165 N.E. 68 (1929); *Rueb v. Rehder*, 24 N.M. 534, 174 P. 992 (1918); see: *Van Daele v. Vinci*, 51 Ill. 2d 389, 282 N.E. 2d 728 (1972).

It would be, therefore, an exercise in dilatory formalism were the Court to defer its own action to await further action from within the Association. There is no need of any additional expertise, as might be brought to bear by the further internal functioning of the Association, to enable the Court to recognize that the Association's

"... functionaries have operated outside their proper sphere; thus the member's legal status has not been altered, there is nothing to appeal from, [within the Association]"

and, hence, the Court may justifiably conclude that it should

"... secure the plaintiff his rightful position at once."

See: 76 Harv. L. Rev. 983 (supra, n. 3) at p. 1073.

Further, the Court would be perpetrating a special anomaly were it in the instant circumstances to require that plaintiff exhaust procedures internal to the Association since the actions here taken in violation of the Association's by-laws were not confined within the Association but reached outside to involve other public and private agencies. The report containing the conclusions of the Association's Ethics and Discipline Committee was transmitted to external bodies having power, tangibly and intangibly, to impair Dr. Gashgai's opportunity to earn a livelihood and practice his chosen profession; indeed, one of these agencies, relying on the Committee's report, had already taken steps in this direction by subjecting Dr. Gashgai's invoices to "constant surveillance."

In such context, as the United States Court of Appeals for the District of Columbia Circuit stressed in *Marjorie Webster Junior College, Inc., v. Middle States Association of Colleges and Secondary Schools, Inc.*, 432 F.2d 650 (1970):

"The increasing importance of private associations in the affairs of individuals and organizations has led to substantial expansion of judicial control over 'The Internal Affairs of Associations not for Profit.' Where membership in, or certification by, such an association is a virtual prerequisite to the practice of a given profession, courts have scrutinized the standards and procedures employed by the association notwithstanding their recognition of the fact that professional societies possess a specialized competence in evaluating the qualifications of an individual to engage in professional activities. . . .

"... the extent to which deference is due to the professional judgment of the association will vary both with the subject matter at issue and with the degree of harm resulting from the association's action." (pp. 655, 656)

See also: *Falcone v. Middlesex County Medical*

Society, 34 N.J. 582, 170 A.2d 791 (1961).⁵

The judgment of the Superior Court is affirmed.

The entry is:

Appeal denied.

All Justices Concurring.

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REFERENCES

1. The Justice (1) prohibited the "... circulating, forwarding or distributing the report of the ... Committee dated March 27, 1974 as it pertains to plaintiff, and" (2) ordered that each of the defendants, except for their attorneys of record, "... expunge from their records said report and any references thereto, that copies of this Order and the Findings of Fact and Decree of ... [the] Court be sent by Defendants to each person or organization to whom the original report was sent, and that all copies of said report now in the hands of defendants or within their control, now or in the future, except one copy in the hands of defendants' attorneys of record, be finally and permanently suppressed."
2. These by-law violations were: (1) "The By-laws of the De-

fendant Association provide that the Defendant Committee shall urge disposition of ethical complaints at the local County Society level, by County Society officers. Defendant Trembly and the Defendant Committee made no effort to refer the complaint of the Department of Health & Welfare in Plaintiff's case to the appropriate Component Society, the Kennebec County Medical Society." (2) The Ethics and Discipline Committee wrongly undertook the *investigatory* tasks involved in the requests made to it by the State of Maine Department of Health and Welfare since "[t]he By-laws of the Defendant Association provide that the Defendant Committee shall have 'no power or authority' to act upon any complaint or claim or case referred to it where the facts of the complaint are or may become the basis for an action in tort against the doctor whose conduct is being investigated until and unless any case which should arise is finally disposed of." (3) The Ethics and Discipline Committee wrongly undertook the *investigatory* tasks involved in the requests made to it by the State of Maine Department of Health and Welfare since "[t]he By-laws of the Defendant Association provide that the 'primary duty' of the Defendant Committee is to give careful consideration and study to methods and practices which tend to eliminate justifiable complaints against the profession or individual members of the medical profession on the desirability of following those recommended methods and practices."

3. 76 Harv. L. Rev. 983, et seq. contains an extensive review of the matter in its evaluation of "Developments in the Law" concerning "Judicial Control of Actions of Private Associations."
4. These "exhaustion" doctrines are somewhat related insofar as they both reflect an underlying judicial policy of deferring to an expertness which courts attribute to the other bodies involved.
5. In *Falcone* the Court made the cogent observation: "When courts originally declined to scrutinize ... practices of membership associations they were dealing with social clubs, religious organizations and fraternal associations. Here the policies against judicial intervention were strong and there were no significant countervailing policies. When the courts were later called upon to deal with trade and professional associations exercising virtually monopolistic control, different factors were involved. The intimate personal relationships which pervaded the social, religious and fraternal organizations were hardly in evidence and the individual's opportunity of earning a livelihood and serving society in his chosen trade or profession appeared as the controlling policy consideration." (p. 799)

MAINE BLUE CROSS AND BLUE SHIELD NEWS — *Continued from Page 69*

and a maximum of \$30,000 accumulated over two or more benefit periods.

3. Blue Alliance does not pay the difference between your Blue Cross allowance for room and board and the hospital's daily room charge.

For more information about the program, contact David ten Eyck, Maine Blue Cross and Blue Shield, 110 Free Street, Portland, Maine, 04101, Telephone 775-3536.

Reminder to M.M.A. Members

CONTINUING MEDICAL EDUCATION ACTIVITY REPORT

The bylaws of the Maine Medical Association were amended in June of 1973 as follows: Chapter I, Section 11, — "Each member of the Maine Medical Association shall be required to report his activities in continuing medical education every year according to a format provided by the Committee on Continuing Medical Education."

Only active, dues-paying members are required to report this year.

Please fill in your activity report promptly and return to the M.M.A. office, P.O. Box 250, Brunswick, Maine 04011.

News, Notes and Announcements

CENTRAL MAINE GENERAL HOSPITAL and ST. MARY'S GENERAL HOSPITAL announce

"CLINICAL PROBLEMS IN MEDICINE AND SURGERY"

A Regional Postgraduate Course

March	24, 1976	ADVANCES IN IMMUNOLOGY Dr. Robert S. Schwartz
April	21, 1976	RECENT ADVANCES IN THE MANAGEMENT OF SHOCK Drs. Herbert J. Levine and Stephen N. Martyak
May	19, 1976	RECENT ADVANCES IN NEURO- SURGERY AND NEUROLOGY Drs. Bennet M. Stein, John F. Sullivan and Samuel M. Wolpert
June	9, 1976	CLINICAL PROBLEMS IN GYNE- COLOGIC ENDOCRINOLOGY Drs. Martin M. Farber and Robert D. Kennison

TIME: 2:30 to 6:30 p.m. Wednesdays

PLACE: Main Auditorium, Central Maine Vocational Technical Institute (CMVTI), 1250 Turner St., Auburn, Maine.

REGISTRATION FEE: \$15.00 per session. Residents and medical students, no fee. This program is supported in part by Area Health Education Center funds.

This Continuing Medical Education offering meets the criteria for credit in the Category 1 for the Physician's Recognition Award of the American Medical Association.

REGISTRATION FORM

(please print or type)

- ☐ Sessions
☐ Medical Student/Resident

CENTRAL MAINE REGIONAL POSTGRADUATE COURSE

NAME

ADDRESS ZIP

Please make check payable to Tufts University and mail to:
ROBERT F. KRAUNZ, M.D., Course Coordinator, Central Maine General Hospital, Lewiston, Maine 04240.

Physicians Invited to Attend 55th Annual Meeting of New England Hospital Assembly Incorporated

The malpractice crisis, the health policies of Canada and the United States, care of the dying patient, the contradictions of health regulation, and current prospects for national health insurance are among topics to be featured during the 55th annual meeting of the New England Hospital Assembly Incorporated, to be held in Boston March 30-April 1, 1976 and to which physicians from throughout New England are invited.

"Public criticism and accelerating regulation make it more important than ever that physicians join their colleagues in the health professions to consider, discuss and debate what's happening to health care," said John Waters, President of the New England Hospital Assembly Incorporated.

Approximately 15,000 persons are expected for the meetings for which registration is free. All programs are held in Boston's John F. Hynes Veterans Auditorium and in the adjoining Sheraton-Boston Hotel.

Four attorneys, one of whom is a Boston Superior Court judge, will address, "The Myths and Realities of Malpractice — from Operating Room to the Court Room" on April 1. During

the afternoon on the same day, Ned Cassem, M.D. of Massachusetts General Hospital and Florence Wald, R.N. of New Haven, Connecticut will discuss, "Death and Dying — The Challenge."

The keynote address on Tuesday, March 30 opens the three-day annual meeting and features Prof. Malcolm Taylor, Consultant to the Canadian Ministry of Health. He will review national health policy, and the impact of political and economic factors on health institutions and professionals.

Other program topics during the 55th annual meeting treat the identity crisis in nursing — who is the director?; the national health planning act — who will be running the health care system?; responsibility to whom and for what, with emphasis upon viewpoints of the Joint Commission, planners and regulators; patient education; and an up-to-the-minute look at the prospects for national health insurance, as viewed by H. Robert Cathcart, chairman of the board of trustees of the American Hospital Association.

In addition to general session forums, the annual meeting will be the site of concurrent meetings conducted by more than 40 New England allied health organizations.

Program and registration information is available from the New England Hospital Assembly Incorporated, 91 Crest Avenue, Chelsea, Massachusetts 02150.

Biofeedback Training Seminar and Workshop

A Biofeedback Training Seminar and Workshop will be held in North Conway, New Hampshire on April 2, 3, and 4. This seminar is clinically and practically oriented, and will provide the medical practitioner with both the basic rationale to Biofeedback treatment and familiarization with techniques and instrumentation. Biofeedback is currently being used with good success in the treatment of migraine and other headache disorders, Raynaud's disease, cardiac arrhythmias, hypertension, sexual dysfunction, and other disorders. The tuition for the seminar will be \$85.00 for physicians and \$25.00 for medical assistants. The physician's office assistant usually hooks up and monitors the patient, and therefore the opportunity for their orientation is included in the seminar.

Address inquiries to Richard A. Levy, M.D., Biofeedback Treatment Center, 128 Chadwick Street, Portland, Maine 04102.

Student Health Center Assistant Director

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County Society Notes

York

The October meeting of the York County Medical Society was held on October 15, 1975 at the York Hospital, York Village, Maine. This meeting was changed from October 8 because several of the members were away at the meeting of the American Academy of Family Physicians in Chicago. The format of this meeting was the same as usual and consisted of a Social Hour from 6:30 p.m. to 7:30 p.m., Dinner, Speaker and Business Meeting to follow.

The featured speaker, introduced by Dr. Carl Richards, President of the York County Medical Society, was James F. McMichael, President of Unionmutual Management Corporation, Portland, Maine. His subject was "Investing: Does It Still Make Sense?" All those present wholeheartedly agreed on the significance, importance and value of this stimulating presentation. It is interesting to note that copies of his talk have been requested. We are frankly disappointed that more members don't attend these meetings which are most interesting.

Following the speaker, the Business Meeting was presided over by Dr. Richards. In the interest of time, the minutes of the last meeting were dispensed with. A report of the Annual Meeting of the House of Delegates of the M.M.A. held at the Treadway-Samoset Resort, Rockport, Maine in June was also dispensed with. Our President then brought up the increase in dues which are as follows: \$250.00 American Medical Association dues for 1976 and \$250.00 Maine Medical Association dues for 1976 (including York County Medical Society dues).

The applications of Drs. Richard H. Nealis and Gerald T. Keegan were accepted for membership in the York County Medical Society. All members were urged to return the questionnaires regarding participation on Committees of the Maine Medical Association.

The following announcements were made:

1. The Annual Meeting of the York County Medical Society and its Auxiliary will be held at the Cascades Inn, Saco, Maine, on January 7, 1976 with a format similar to last year.

2. The proposed Diabetes Detection and Education Program for York County was announced by Dr. Melvin Bacon, Chairman of the Diabetes Committee of the Maine Medical Association. In brief, he will be assisted by Beverly Tirrell, R.N., President of the York County Public Health Nurses Association with members of the York County Medical Society with their town, city or area Chairmen, Health Councils, hospitals, nursing homes, nurses, members of the laity, etc. An extensive Blood Sugar and Blood Pressure Screening Program will be conducted in all industries, schools and general programs in all town, city or areas of York County.

3. The House of Delegates Meeting is to be held on Saturday, December 13, 1975 at the Mid-Maine Medical Center (Thayer Hospital), North Street, Waterville, Maine. Registration will be at 12:30 p.m.; Dinner — 1:00 p.m.; Business Meeting — 2:00 p.m.

The meeting was adjourned in record time at 9:00 p.m. with 20 physicians and 2 guests present.

MELVIN BACON, M.D., *Secretary*

Penobscot

The October 1975 meeting of the Penobscot County Medical Society was held at the Heritage Inn in Millinocket, Maine. An outstanding dinner preceded the business and scientific portions of the meeting.

The meeting was opened by the President, Dr. Thornton W. Merriam, Jr. and the minutes of the May 1975 meeting were read and approved.

Several guests in attendance were then introduced to the membership.

Dr. Merriam presented a report of the Executive Committee of the Maine Medical Association. Dr. Merriam is the representative from our district to the Executive Committee of the Maine Medical Association, and his report represented an effort to keep

the membership informed as to the work and discussions of the Executive Committee. He noted that dues of the M.M.A. have been increased to \$200.00 per year. It was noted that Governor Longley has appointed a Medical Malpractice Commission and Dr. Francis I. Kittredge is a member. The Health Planning and Resources Act was discussed, and it was noted that hearings would be held in the future to determine the composition of the combination consumer-provider group. Finally, it was noted that the cost of retaining a lobbyist for the Maine Medical Association for the past year amounted to approximately \$19,000.

Under old business, the Health Screening Program of 1975, under the direction of Sen-Cit, was approved.

It was recognized that a PSRO for the State of Maine was approved.

Under communications, the following were noted. Dr. James Bates is actively looking for an associate to practice in Eastport. Next, it was noted that the American Medical Association dues were going to be increased. Also, a request for a representative from our Society to the Diabetes Committee for 1975 was made. Anyone interested in this position should contact President Merriam. Lastly, a request from the Maine Medical Association to the membership asking for volunteers to serve on the special and standing committees for the coming year.

A motion was made by Dr. Dexter J. Clough, 2nd which stated the following: "Whereas the term malpractice is a misnomer as applied to insurance, be it resolved that the name of the Committee of Medical Malpractice of the Maine Medical Association be changed to the Committee on Professional Liability." This motion was seconded and passed.

Dr. Clough made a second motion which stated the following: "Whereas the name of the Pine Tree Organization for Professional Standards Review is an inappropriate name, that the name be changed to the Maine State Organization for Professional Review." This motion was seconded and defeated.

A motion was made, and it was seconded and passed that the residents of the Family Practice Residency Program at Eastern Maine Medical Center be encouraged to apply for membership in the Penobscot County Medical Society and that this organization pay the cost of these individuals' meals.

The applications for membership into the County Society for the following physicians were presented: Drs. Sidney R. Block, R. Russell Lang, A. Dewey Richards, Timothy S. Witwer, John J. McDevitt, 4th, Michael B. Solomon and Alfred Berg. Each application was approved.

The scientific portion of the meeting was presented by Dr. A. Dewey Richards concerning the Family Practice Program at Eastern Maine Medical Center. He described the program as it is presently constituted, and the plans for the future. A question and answer session then followed.

As there was no further business, the meeting was adjourned.

PHILIP G. HUNTER, M.D., *Secretary*

Androscoggin

The regular meeting of the Androscoggin County Medical Society was held at Steckino's Restaurant in Lewiston, Maine on October 16, 1975. The meeting was called to order by Dr. Stanley D. Rosenblatt, Vice-President, at 8:00 p.m., with 33 members present.

The September minutes were approved as read.

Regarding Mental Health Committee: Drs. Ake Akerberg, Venkat R. Sundaram and Najib M. Pandya appointed. Dr. Hampshire is not a member of the County or State Society.

The applications of Drs. In Guk Kim and Paul Atallah were approved for membership.

The application of Dr. Gerald Davidson for membership is to be reviewed by the Credentials Committee and voted on at the next meeting.

Dr. Carleton H. Rand was voted to Honorary membership. Dr. Ralph Zanca was voted to Affiliate membership. Dr. Merton M. Flanders' application for Affiliate membership was tabled.

Drs. Michael J. Harkins' and Charles W. Steele were voted to Senior membership. Dr. Jan Knoppers' application for Junior membership was disapproved.

A nominating committee was appointed: Dr. Gerard L. Morin, Chairman; Dr. Thomas F. Shields and Dr. Gilbert R. Grimes are the other members of the committee. They are to bring a slate of officers and delegates at the December meeting.

Dr. Rosenblatt introduced the speaker of the evening, Dr. H. Douglas Collins, Director of Family Practice Program. He stated that Family Practice is growing as a specialty, second to Internal Medicine. Emphasis on ambulatory care stressed. Criteria for Residency was outlined. Funding becoming a problem; third-party payers and hospitals picking up the tab. V.A. contributions are declining. Teaching problems mentioned. Present curriculum given as well as cost per resident. Program in Maine not tied (affiliated) to any medical school.

A question and answer period followed.

Meeting adjourned at 9:20 p.m.

DONALD L. ANDERSON M.D., *Secretary pro tem*

Oxford

The semi-annual meeting of the Oxford County Medical Society was held on October 29, 1975 at the Rumford Community Hospital. Twenty-one members and one guest were present. The meeting began at 5:30 p.m. and the business meeting was called to order by the President, Dr. Stephen Dewing. Motion was made and carried to dispense with the reading of the minutes of the previous meeting.

Communications

Letter from Dr. Robert Van Hoek, Acting Administrator, Department of HEW, was read putting the Society on notice of the conditional designation of the PTO as the PSRO for the area.

Letter from Dr. Euclid M. Hanbury, Jr. was read stating that the Executive Committee of the M.M.A. had instructed him to inquire of the Societies into the existence of Mental Health Committees.

Letter from Dr. James C. Bates, Administrator of the Eastport Memorial Hospital, was read requesting reference of physicians looking for a practice in Maine to their hospital.

A letter from Raymond T. Sullivan, Jr., Regional Director of the AMA, calling for additional enrollment in the AMA and comparing the AMA dues to that of other trade unions was read.

A letter from Medical Care Development, Inc., was read which asked for endorsement of "Guide to Blood Pressure Detection and Treatment."

There was no old business.

New Business

The Chairman of the Nominating Committee, Dr. Linwood M. Rowe, presented the nominations of the following slate of officers:

President: Dr. Adwaita K. Ganguli, Rumford

Vice-President: Dr. Kenneth G. Hamilton, Norway

Secretary-Treasurer: Dr. Robert S. Bausch, Norway

Delegates to the M.M.A. House of Delegates: Drs. David L.

Phillips, Rumford and Kenneth G. Hamilton. Alternates:

Drs. James A. Edmond, Rumford and Robert W. Scarlata, Norway

Councillors: Drs. Harry L. Harper, South Paris, Dexter E.

Elsemore, Dixfield and Eugene Gorayeb, Rumford

It was moved and seconded that the secretary cast one ballot for the election of this slate.

The applications of Drs. Venkat Sundaram, Om Wadhwa and Usha Wadhwa were introduced as having been approved by the Councillors. On motion, it was voted unanimously to accept them into membership. Dr. Sundaram is an affiliate member, being a member of Androscoggin County.

On motion, the nomination of Dr. Sundaram was made and carried, appointing him to Chairmanship of the County Mental Health Committee. On motion, Dr. Eugene J. Gorayeb was elected as the representative for this county to speak at the appropriate regional meeting of the legislative hearings of the Malpractice Commission, which will be held during the upcoming special session of the legislature.

Dr. Dewing then introduced Dr. Euclid M. Hanbury, Jr., President of the M.M.A., who spoke concerning affairs of great interest to the membership and answered questions.

The items discussed included: the Malpractice situation, the current status of the Medical School for Maine and its alternatives, the EMS directorship, recent decision to add major medical coverage to our present BC-BS Group Plan, the recent IRS decision to make a test suit of one-man corporations in Maine, the Health Systems Agency Act and its problems, and the deletion of the annual session registration fee. An enthusiastic discussion was enjoyed.

The group then adjourned to the social hour and dinner, which was enjoyed by all.

DAVID L. PHILLIPS, M.D., *Secretary*

Lincoln-Sagadahoc

The regular monthly meeting of the Lincoln-Sagadahoc County Medical Society was held on October 21, 1975 at the Ledges Inn in Wiscasset, Maine. There were seventeen members and seventeen guests present.

The meeting was called to order at 8:50 p.m. by the Vice-President, Dr. David S. Hill. The minutes of the September meeting were read by Dr. Bostwick and accepted without change.

The Board of Censors proposed the names of Dr. Babette H. Lenna, East Boothbay, Maine and Dr. Frank W. Sheldon, R.F.D. #1, North Edgecomb, Maine, for active membership. These recommendations were unanimously approved by the members present.

Dr. Belknap moved and Dr. Leck seconded the motion that county society dues for 1976 be set at forty dollars (\$40). The motion was passed.

There was no other business. The ladies retired to another room for their Auxiliary meeting, and Dr. Dixon introduced Dr. Gerry Hayes, who spoke on the erythrocyte sedimentation rate and led a discussion of temporal arteritis.

The regular monthly meeting of the Lincoln-Sagadahoc County Medical Society was held at The Ledges in Wiscasset, Maine on November 18, 1975.

There were thirty-eight members and guests present to hear a fascinating talk on Low Back Pain by Dr. Barbara Stimson of Owl's Head.

The meeting was called to order by the President, Dr. Ralph C. Powell at 8:30 p.m. The Secretary read the minutes of the October meeting, and they were accepted as read.

Dr. Robert H. Dixon then introduced the speaker.

There was no old business.

New business: The secretary read the text of H.P. 176 — L.D. 200, "An Act Relating to the Prescribing and Dispensing of Drugs." Dr. Richard C. Leck then described a new law on disclosure of formerly privileged information in medical records. He stated that the M.M.A. policy for Blue Cross/Blue Shield will provide Major Medical coverage next year at a slight increase in cost. He announced that the new State Director of Emergency Medical Services will speak at the Interim Session of the House of Delegates in December.

Dr. Leck described at length the Health Systems Agency being instituted in this State. Meetings will be held on the 25th of November (at Valle's Steak House, Exit 8 on the Maine Turnpike for this region) to hear proposals for nominations to the Board of the H.S.A. The grave implications of the Health Planning and Resources Development Act were discussed.

Dr. Powell appointed a nominating committee to bring in a slate of officers for consideration at next month's meeting: Drs. Louis Bachrach, Frank O. Avantaggio, Jr. and John F. Andrews.

Dr. Leck moved and Dr. Bachrach seconded the motion that the December meeting be a minimal business session and that the major emphasis be placed on a social affair to include spouses. The motion was defeated.

The meeting was adjourned at 9:30 p.m.

GEORGE W. BOSTWICK, M.D., *Secretary*

Cumberland

The November meeting of the Cumberland County Medical Society was held at the Red Coach Grill in Portland, Maine on November 20, 1975.

Applications for Membership - First Reading

Drs. James D. Miller and J. Mark Kjeldgaard.

Applications for Membership - Second Reading

Drs. David W. Haskell, Mary O. Morse, Robert L. Morse, Doris S. Pennoyer, Stanley A. Rosenberg and Gerald S. Veregge.

New Business

Dr. Walter B. Goldfarb gave a report on the Cumberland County Medical Society answering service.

The Treasurer's Report was presented covering the months of June 1975 to November 1975. Expenditures were \$23.98 under what was spent last year at this time.

Announcements

There have been many calls to Cumberland County physicians requesting prescriptions for Tussionex.[®] These calls are being made by drug abusers and the members were cautioned to resist such requests.

Continuing Medical Education Activity Reports are due.

Changes in AFDC billing procedures, effective March of 1976 were discussed by the President, Dr. Robert E. McAfee.

Program

The membership heard from three speakers:

1. Mr. John E. Burrill, R.Ph., Executive Secretary of the Maine Pharmaceutical Association, who spoke on the subjects:

- a. Maximum allowable costs.
- b. Product substitution.
- c. Amphetamine control.

2. Henry Pollard, D.M.D., President of the Maine Dental Association and immediate past president of the Maine Dental Service Corporation, who spoke on prepaid Dental Insurance.

3. Dr. Douglas R. Hill, C.C.M.S., Representative to the

Maine Medical Association Executive Committee, who reported on the most recent meeting of the State Executive Committee.

WESLEY J. ENGLISH, M.D., *Secretary*

Kennebec

The Council of the Kennebec County Medical Association met on November 13, 1975. In attendance were Drs. Hiebel, Hayes, Feagin, Moore, Barron and Towne. Invited delegates were Drs. Davis, Gould and Executive Committee Member, Dr. Chamberlin.

The request of Drs. McKinley and Collins to transfer from the Aroostook County Medical Society were noted and Dr. Feagin will contact that Society for their good standing. The application of Dr. Robert I. Roy was read.

The next item of business to be considered was the bylaws. It was decided to present the bylaws as they currently exist to the membership at the next meeting and at that time to send them to the law department of the AMA to see if they see anything in them to object to.

The final item of business was the report of Dr. Richard T. Chamberlin. He had two primary areas to report on. First, the Malpractice Commission which will be holding public hearings in the near future, and Dr. Chamberlin felt that we should have a representative of the County Society to present the physicians' case before this Commission. The whole issue was vigorously discussed and no particular member was selected at this point in time to step forward. The second item of discussion was the Health Services Act and Dr. Chamberlin discussed with the Council the ins and outs of that situation. Again, no action was taken. There were apparently no items requiring vote at the end of the meeting that Dr. Chamberlin thought that the delegates should be instructed regarding, so the meeting adjourned at 10:30 p.m.

O. THOMAS FEAGIN, M.D., *Secretary*

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Number 4

Status of Intensive Respiratory Care for Acute Respiratory Insufficiency*

E. CONVERSE PEIRCE, 2ND, M.D.**

ABSTRACT

Perhaps 75,000 adults die yearly in the U.S. from ARI. Patients have stiff lungs and low arterial oxygen tension, little improved by high inspiratory oxygen levels (FiO_2). The high pressures and FiO_2 levels required are themselves damaging. ECMO can buy time and prolong life up to at least 3 weeks, providing potential salvage when ARI is reversible with time, continuing respiratory nursing care, or specific therapy. We do not yet know what patients should be offered ECMO but are attempting to answer this through a rigorous collaborative study supported by the National Heart and Lung Institute. A membrane lung (which causes tolerable blood damage) appears necessary for prolonged perfusion. Veno-arterial perfusion (using peripheral cannulation) is the preferred mode since most patients have concomitant circulatory failure and an elevated pulmonary artery pressure. The most important problem is avoidance of hemorrhage. A low dose of heparin is given continually while the effect is monitored at least hourly. Other serious problems include fluid balance management, renal failure, and infection. More than 170 patients have been treated with ECMO worldwide by at least 63 groups using 8 different membrane lungs. Thirty-five percent have improved sufficiently to permit ECMO to be discontinued. Twelve percent have recovered. More careful screening of cases and acquisition of data are required before the value of ECMO for ARI can be determined.

INTRODUCTION

At least a quarter of a million cases of acute re-

spiratory insufficiency (ARI) occur in the United States each year and perhaps 75,000 of the patients with this disease die. There is great similarity in the pathophysiology and pathology of various cases because the lung has a limited number of responses it can make to injury:

ACUTE RESPIRATORY INSUFFICIENCY (ARI) COMMON PATHOPHYSIOLOGY

- Poor lung compliance
- Elevated vascular resistance
- Restricted oxygen exchange
 - Large "physiologic" shunt causing
 - Large alveolar-arterial (A-a) gradient

ARI is a disease of many causes as shown in the table:

SOME ETIOLOGIC FACTORS

- Trauma, transfusion, or perfusion
- Infection: Bacteria, virus, protozoa
- Chemical: Aspiration, oxygen, burns
- Embolic: Blood clots, fat
- Cardiac failure: Pulmonary edema

Many causes of ARI are iatrogenic or at least preventable:

SOME PREVENTABLE CAUSES OF ARI

- Aspiration of acid-gastric contents
- Oxygen toxicity from oxygen over 60%
- Prolonged use of non-membrane oxygenators
- Failure to use microfilter for transfusions
- Overuse of broad spectrum antibiotics
- Delay in treating cause of shock
- Failure to recognize thrombophlebitis

Aspiration of acid-gastric contents in the hospital is one of the most important causes of ARI and the mortality rate is very high. Many of the aspirations are actually precipitated by such things as induction of anesthesia. The judicious use of neutralizing

*Presented at the First Annual Maine Biomedical Science Symposium, Augusta Civic Center, March 14-15, 1975.

**Department of Surgery, Mt. Sinai School of Medicine of the City University of New York and Veterans Administration Hospital, Bronx, New York.

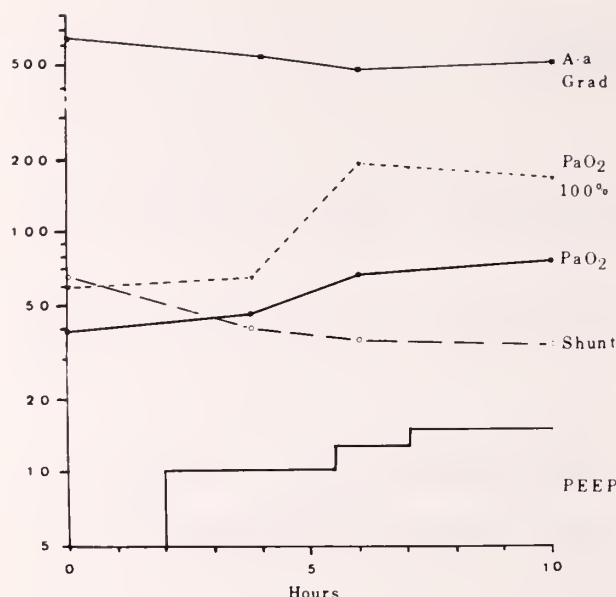


Fig. 1. This illustrates respiratory data from a patient recently perfused for 16.5 days for ARI.¹⁰ On 5 cm of PEEP, the PaO₂ on 100% oxygen was only 60 mm Hg, the shunt was 65 percent, and the alveolar-arterial (A-a) gradient nearly 650 mm Hg. As PEEP was increased progressively to 15, there was marked improvement with the PaO₂ on 40% oxygen rising from 39 to 74 mm Hg, the PaO₂ on 100% oxygen reaching nearly 200 mm Hg, the shunt decreasing to 35%, and the A-a gradient falling to about 500 mm Hg.

antacids under circumstances where vomiting may occur can greatly reduce the morbidity and mortality of any aspiration that does occur since the danger is more or less directly proportional to the acidity of the aspirate. More judicious use of oxygen with strict avoidance of inspiratory oxygen saturations greater than 60 percent would moderate or prevent the contributory damage of oxygen toxicity seen in many terminal respiratory cases.

The elements of modern intensive respiratory care are listed:

BASIC MODERN INTENSIVE RESPIRATORY CARE

- Intensive nursing care
(Especially turning of patients)
- Volume cycled ventilation
- Positive end expiratory pressure (PEEP)
- Proper humidification
- Aseptic airway management
- Fluid restriction, diuretics, colloid
- Minimum percent oxygen
- Appropriate antibiotics only

Respiratory nursing care is perhaps the single most important element of the intensive regimen.¹³ To avoid progressive edema, atelectasis, and consolidation, patients must religiously be turned so that they spend time on each side and on or nearly on their stomach. Of special interest is positive end expiratory pressure (PEEP). This potent tool, which has revolutionized intensive respiratory care, must be used with care to avoid circulatory embarrassment in patients who may be volume depleted,

a situation especially likely where dehydration has been used as a principle method of treatment of ARI. PEEP prevents alveolar collapse by increasing the functional residual capacity of the lung. Significant improvement in function is possible in even very stiff lungs (Fig. 1). Even without actual consolidation or frank fibrosis, oxygen exchange will usually be improved by PEEP. Failure to obtain such improvement with PEEP is a very ominous sign as the preperfusion data of the next table attest.⁵

ASPIRATION PNEUMONIA

Suicide attempt

15-year-old

Duration before perfusion 2 weeks

PaO₂ 40 mm Hg on 100% oxygen

Compliance 10ml / cm H₂O

No improvement with PEEP

Each time PEEP was tried, there was a disproportionate rise in peak pressure and no improvement in pulmonary function. This patient finally died after 21 days of ECMO without evidence at anytime of respiratory improvement. There was an alveolar-arterial (A-a) gradient of more than 600 mm Hg and a calculated venous shunt averaging about 70 percent. Clearly the lung was irreversibly damaged before the perfusion both by the initial aspiration and by nearly two weeks of 100% oxygen.

RATIONALE OF ECMO

Notwithstanding the impressive advances in intensive respiratory care made in recent years, many patients cannot be adequately supported and succumb after inexorably progressive hypoxia. Among these patients there are probably candidates for new and experimental forms of treatment such as extracorporeal membrane oxygenation (ECMO).^{2,6}

For two decades, the membrane lung has been of interest only to a group of hard-headed and persistent investigators.^{7,8,9} The vast majority of all extracorporeal procedures have been carried out with non-membrane oxygenators. These devices have been expedient for the usual perfusions required in open heart surgery. In 1972, a patient of Dr. Hill, et al survived after a long-term perfusion of nearly five days using a membrane lung. The patient had severe ARI following repair of an aortic tear that resulted from an automobile accident.³ Since then membrane lungs have been used to provide respiratory and circulatory support for as long as 21 days.^{2,5} There can be no doubt that the membrane lung is the device of choice for any prolonged perfusion needs.⁸ Generally speaking, however, ECMO is not a treatment for ARI but only buys time during which respiratory function of the patient may or may not recover. The important thing is whether or not the respiratory disease is reversible within a reasonable period. Unfortunately, we do not yet know which conditions are reversible. Only now that we are able to prolong a patient's life with

severe ARI are we beginning to accumulate such vital information as the natural course of the disease. It seems probable of course that more conditions will be reversible if the damage of high respiratory inflation pressures and high oxygen tensions can be avoided, things that are possible when the patient is supported by ECMO.

SELECTION OF PATIENTS

The results of ECMO to early 1974 collected by Gille are shown:

PERFUSION FOR ARI

Results to early 1974 (Gille)

Number of cases	167
Duration of perfusion to 21 days	
Improved 35%	58
Recovered 12%	19
Varieties of Lungs Used	8
Number of separate groups	63

It seems that some patients will recover because of ECMO. Unfortunately, others may develop complications, such as severe hemorrhage, as a result of ECMO, that make recovery less likely. Whether or not this modality of treatment will have a net benefit is not known yet. For this reason a National study supported by the National Heart Lung Institute requires that patients qualifying for treatment with ECMO be randomized so that some of them will be controls.¹²

Improvement in the selection of patients and in the techniques of long-term perfusion may provide improved results. Unfortunately, it is still too early to tell how the National study will progress.

Criteria for the selection of patients were of necessity chosen somewhat arbitrarily and briefly are as follows:¹²

NATIONAL PROTOCOL CRITERIA FOR ADMISSION OF PATIENTS TO STUDY

1. Rapid deterioration and
PaO₂ 50 mm Hg or less for 2 hours with
FiO₂ of 1.0 and PEEP of 5 cm H₂O or higher
2. Full therapy for 48 hours and
 - a) PaO₂ 50 mm Hg or less for 12 hours
on FiO₂ of 0.6 and PEEP of 5 cm H₂O or higher
 - b) Shunt of more than 30%

These patients are generally sicker than would have been true for the same degree of hypoxia several years ago. All of them must have received the best in intensive respiratory care including a trial of PEEP. This may account for current difficulty in entering many patients in the National study.

Patients must be identified as having potentially severe ARI before their problem is irreversible. If one waits for clear cut evidence of cerebral or cardiac hypoxia or insists on a prolonged trial of 100% oxygen, the chance of salvage with ECMO becomes minimal. Patients sick enough to require respiratory support should be placed on 100% oxygen for 15 minutes each day, and the alveolar-arterial gradient (A-a gradient) determined. Any

gradient with an A-a gradient above 300 mm Hg signals impending severe ARI. A rough pulmonary insufficiency index may be calculated by plotting the A-a gradient each day and assigning one unit for each day there is a 100 mm Hg excess over 300 for the A-a gradient. For example, if a patient had an A-a gradient of 500 for 3 days, the index would be 6. For a discussion of this method, see the article by Bartlett, et al.¹

TECHNIQUE OF ECMO

A well-trained team able to supply continuous, round the clock, care for several weeks is required. The team must have expertise in intensive respiratory nursing, perfusion, vascular surgery, anesthesiology, and certain aspects of hematology. Continuous laboratory backup is necessary. Generally, two to four persons must be with the patient at all times. Hospitals without special experience and facilities should give serious consideration to referring potential ECMO patients to one of the National study teams in the northeast:

Warren Zapol, M.D. or Henning Pontoppidan, M.D.

Massachusetts General Hospital, Boston, Massachusetts 617-726-8975

Philip A. Drinker, Ph.D. or Nicholas E. O'Connor, M.D.

Peter Bent Brigham Hospital, Boston, Massachusetts 617-734-8000

E. Converse Peirce 2nd, M.D., C. W. Bryan-Brown, M.D. or Daniel J. Krellenstein, M.D.
Mount Sinai Hospital, New York, N.Y. 212-650-6189

(This group can also accept veterans at the Bronx Veterans Administration Hospital 212-584-9000)

L. Henry Edmunds, Jr., M.D. or Richard Hicks, M.D.

University of Pennsylvania, Philadelphia, Pa. 215-662-2091

Some of the major technical elements of the perfusion are listed in the table:

SOME TECHNICAL CONSIDERATIONS FOR ECMO

Adequate support team
Ability to perfuse for 7 days or more
Peripheral cannulation (proximal and distal for most vessels)
Circuit using membrane lung and capacity up to 6 liters per minute
Monitoring including pulmonary pressures and cardiac output
Control of heparin activity

Our preference is veno-arterial cannulation since many of these patients have concomitant circulatory failure. Veno-arterial perfusion reduces the pulmonary artery pressure (Fig. 2) and provides support for a failing heart. Heparin effect is most

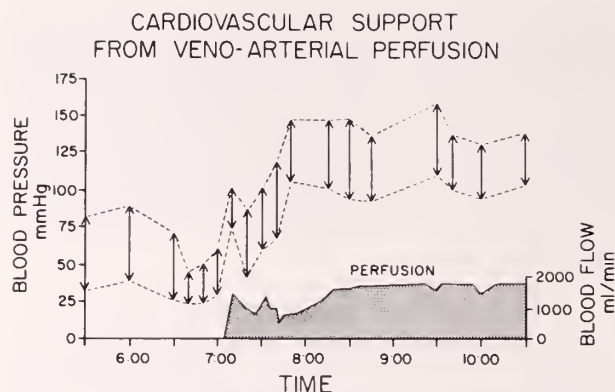


Fig. 2. This depicts data from a 35-year-old woman who developed profound combined respiratory and circulatory failure after open heart surgery to replace three valves. Institution of ECMO permitted stabilization of her circulation as illustrated by the change in blood pressure. In addition to adding about 150 ml of oxygen per minute for respiratory support, the circulatory stabilization permitted institution of PEEP for the first time which resulted in marked improvement in lung compliance so that adequate ventilation was possible. (Reproduced with permission from the Mt. Sinai J. of Medicine¹¹).

easily monitored using the activated clotting time.⁴ This is done at the bedside. The ACT is generally kept below 3 minutes. The dose varies with temperature, urine volume, and many other factors. Five to 40 units per Kg. per hour, given continuously IV, is the usual dosage range. With proper control of heparin, bleeding from incisions, the respiratory tract, and the gastrointestinal tract can usually be moderated if not absolutely controlled.

The plan of treatment is to maintain the arterial oxygen tension about 55 mm Hg. A variety of options are available should the PaO₂ be too low. These are shown in more or less their order of priority:

TROUBLE SHOOTING FOR PAO₂ BELOW 55 MM Hg

Increase PEEP etc.
Increase flow — additional venous cannulation if necessary
Change site of blood return to aortic arch or a branch
Pharmacologic paralysis
Hypothermia

A wide variety of special problems may result from bleeding, renal failure, infection, and the need to provide nutrition.

SELECTED POSSIBLE PROBLEMS

Major hemorrhage
Septicemia
Thrombocytopenia
Disseminated intravascular coagulation
Pneumothorax
Device failure
Renal failure
Cardiac failure
Brain death

Teams must be prepared to provide concomitant hemodialysis, to use hyperalimentation, and to treat such things as hemorrhages and pneumothoraces promptly and effectively.

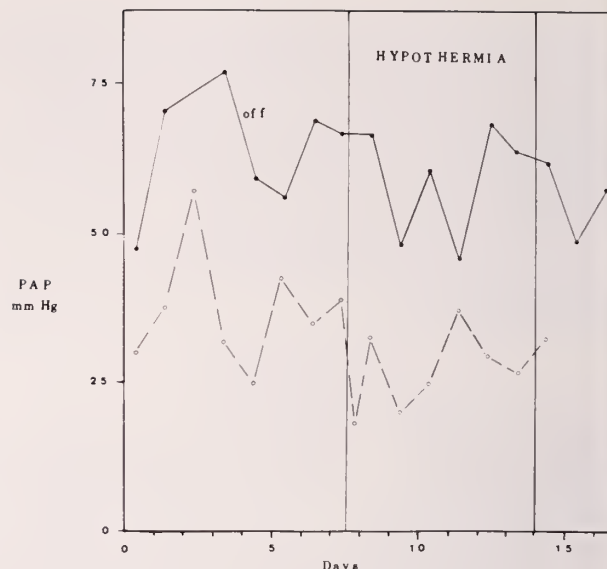


Fig. 3. Veno-arterial perfusion reduces the blood flow through the patient's lungs and consequently moderates the pulmonary hypertension of ARI. This is well illustrated from selected data during a 16.5 day perfusion, part of which was at a temperature of 32° C.¹⁰ Off perfusion the systolic pulmonary pressure was generally over 50 mm Hg. On perfusion at 3.6 to 4.5 liters/minute the pressure was very significantly reduced. This is a major advantage of using ECMO in the veno-arterial mode.

CONCLUSIONS

Extracorporeal membrane oxygenation (ECMO) is promising as a support for patients with severe acute respiratory insufficiency (ARI) who have potentially reversible pulmonary pathology. More careful screening of cases and acquisition of data to determine the natural history of the various respiratory diseases are required before the value of ECMO for ARI can be determined. This modality of therapy must still be considered experimental at the present time.

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Continued on Page 96

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The Pharmaceutical Manufacturers Association represents firms that are significantly engaged in the discovery and development of new medicines, medical devices and diagnostic products. Clinical research is essential to their efforts. Consequently, PMA formulated positions which it submitted on July 11, 1975, to the Subcommittee on Health of the Senate Labor and Public Welfare Committee, as its official policy recommendations. These are the essentials of PMA's current thinking in this vital area.

1. PMA supports the mandate and mission of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research and urges to establish a special committee composed of experts of appropriate disciplines familiar with the industry's research methodology to volunteer its advice to the Commission.

2. PMA supports the formation of an independent, expert, broadly based and representative panel to assess the current state of drug innovation and the impact of existing laws, regulations and procedures.

3. When FDA proposes regulations, it should prepare and publish in the *Federal Register* a detailed statement assessing the impact of those regulations on drugs and device innovation.

4. PMA proposes that an appropriately qualified medical organization be encouraged to undertake a comprehensive study of the optimum roles and responsibilities of the sponsor and physician when company-sponsored clinical research is performed by independent medical investigators.

5. PMA recognizes that the physician-investigator has, and should have, the ultimate responsibility for deciding the substance and form of the informed consent to be obtained. However, PMA recommends that the sponsor of the experiment aid the investigator in discharging this important responsibility by providing (1) a document detailing the investigator's responsibilities under FDA regulations with regard to patient consent, and (2) a written description of the relevant facts about the investigational item to be studied, in comprehensible lay language.

6. In the case of children, the sponsor must require that informed consent be obtained from a legally appropriate representative of the participant. Voluntary consent of an older child, who may be capable of understanding, in addition to that of a parent, guardian or other legally responsible person, is advisable. Safety of the drug or device shall have been assessed in adult populations prior to use in children.

7. PMA endorses the general principle that, in the case of the mentally infirm, consent should be sought from both an understanding subject and from a parent or guardian, or in their absence, another legally responsible person.

8. Pharmaceutical manufacturers sponsoring investigations in prisons must take all reasonable care to assure that the facilities and personnel used in the conduct of the investigations are suitable for the protection of participants, and for the avoidance of coercion, with a respect for basic humanitarian principles.

9. Sponsors intending to conduct non-therapeutic clinical trials through the participation of employee volunteers should expand the membership and scope of its existing Medical Research Committee, or establish such an internal Medical Research Committee, with responsibility to approve the consent forms of all volunteers, designs, protocols and the scope of the trial. The Committee should also bear responsibility to ensure full compliance with all procedures intended to protect employee volunteers' rights.

10. Where the sponsor obtains medical information or data on individuals, it shall be accorded the same confidential

status as provided in codes of ethics governing health care professionals.

11. PMA and its member firms accept responsibility to aid and encourage appropriate follow-up of human subjects who have received investigational products that cause latent toxicity in animals or, during their use in clinical investigation, are found to cause unexpected and serious adverse effects.

12. PMA supports the exploration and development by its member companies of more systematic surveillance procedures for newly marketed products.

13. When a pharmaceutical manufacturer concludes, on the basis of early clinical trials of a basic new agent, that a new drug application is likely to be submitted, a proposed development plan accompanied by a summary of existing data, would be submitted to the FDA. Following a review of this submission, the FDA, and its Advisory Committee where appropriate, would meet with the sponsor to discuss the development plan. No formal FDA approval should be required at this stage. Rather, the emphasis should be on identification of potential problems and questions for the sponsor's further study and resolution as the program develops.

The PMA believes that health professionals as well as the public at large should be made aware of these 13 points in its Policy on Clinical Research. For these recommendations envisage constructive, cooperative action by industry, research institutions, the health professions and government to encourage creative and workable responses to issues involved in the clinical investigation of new products.



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Cardiorespiratory Sequelae in a Model of Sudden Infant Death*

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Sudden Infant Death Syndrome (SIDS) is presumed to result from apnea and has been attributed to a variety of cardiac and respiratory causes. While many of these have been refuted and discarded, the fact remains that more than 10,000 deaths occur from this cause each year.¹ This figure indicates that SIDS alone accounts for more deaths between the ages of one month and one year than any other single cause.²

Numerous theories or hypotheses of possible causal mechanisms having a role in SIDS have been proposed. A sluggish ventilatory system incapable of responding to increased pCO₂ levels in arterial blood may predispose an infant, during normal brief apneic periods, to prolonged apneic periods resulting in hypoxia and acidemia. Such a change in the blood gases in the presence of incomplete development of autonomic control to the heart may induce arrhythmias, hypotension and cardiac arrest. Vagal autonomic control of the heart is present at birth in human infants and most other mammals while sympathetic innervation to the heart is not yet functional.³ Obligate nasal breathing is recognized in infants and other young mammals.⁴ Laryngeal spasm and/or epiglottal obstruction has also been suggested as a possible influencing factor.³ The so-called "dive reflex" also deserves investigation from a developmental standpoint. Stimulation of the mask area of the face, by touch, by a light blast of cool air, or cold water, appears to cause breath-holding and to stimulate vagal and other responses.³

There is histological evidence that the A-V node and bundle of His are undergoing a process of resorption and reorganization during the period coincident with the time course of SID syndrome.⁵ This has led investigators to consider the immaturity of the cardiovascular control systems as the faulty link in SIDS.⁶ Recently, chronic hypoxia has been suggested as a major contributory cause. In relation to this, evidence indicates that medial hypertrophy of small pulmonary arteries occur in SIDS. Hypoxia may be present early in infancy and precede or forewarn events producing cataclysmic SIDS. Chronic hypoxia, recently measured by Naeye as arterial oxygen tension in infants considered as high SIDS risk cases, has further implications. An immature autonomic nervous system in terms of cardiorespi-

ratory control may exist in early infancy, which when appropriately stimulated invoke insufficient, immature or inappropriate cardiorespiratory reflexes thus producing life-threatening results. In this light, we have undertaken an examination of cardiac and respiratory responses to a series of apneic-producing maneuvers. The results which we will discuss will focus on events during and subsequent to apneic periods and on those events which may be responsible for post-mortem findings in sudden infant death.

Young domestic pigs, 3 weeks to 2 months old, were anesthetized with sodium pentobarbital, 30 milligrams per kilogram body weight. A standard lead two electrocardiogram, arterial blood pressure, intrathoracic pressure, and either central venous or right ventricular pressure were inscribed on a multi-channel recorder. Intravascular catheters were inserted via the right femoral artery and the right external jugular vein, respectively. Intrathoracic pressure was obtained from a saline filled catheter inserted into the thorax through a transcutaneous puncture in the fourth intercostal space. Heart rate and mean blood pressure were calculated from pulsatile arterial pressure recordings. Transient apnea was either spontaneous or produced by manual nasal occlusion, or facial immersion in water. Breathing 95% nitrogen: 5% CO₂ presented a hypoxic stress without apnea.

SPONTANEOUS APNEA

We have observed spontaneous apnea in young anesthetized pigs used in previous studies apparently resulting from postural changes. Five pigs of the twenty-six examined in this study exhibited spontaneous apnea. Positional changes from supine to prone resulted in spontaneous apnea, hypotension (blood pressure decreased from a mean systolic and diastolic pressure of 130/85 to 75/35) and bradycardia (mean heart rate of 203 BPM to 70 BPM) with A-V dissociation. Oral gasps produced brief bouts of tachycardia and hypertension lasting for about one minute which reversed to hypotension and bradycardia with A-V dissociation until a second oral inspiratory gasp was made thus repeating the cycle. Return to the supine position reinstated spontaneous breathing in 3 pigs. The remaining two pigs were intubated and put on positive pressure ventilation until spontaneous respiration was resumed. Although none of the animals in this series were allowed to die from this maneuver, previous and subsequent experience in this labora-

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tory with this species indicated that rapid accidental death can occur with such simple positional changes.

NASAL OCCLUSION

Under light anesthesia, simple nasal obstruction (30 sec. to 2 min.) produced apnea, hypotension and marked bradycardia with A-V dissociation in 16 pigs (60%). The mean systolic and diastolic pressures decreased from 140/107 to 95/57 and mean heart rate decreased from 206 to 80. Increase in T wave amplitude and elevated S-T segments were also noted in the ECG.

Nasal occlusion at end-expiration in 11 pigs resulted in violent inspiratory muscle struggles for the first 45 seconds but no attempt at oral breathing. Subsequently, no further attempts to breathe were made until the nares were released. By contrast, nasal occlusion at end-inspiration in 10 pigs was not followed by any respiratory muscle activity until the nares were released.

Animals demonstrating spontaneous apnea or responding to nasal occlusion could be resuscitated by tracheal intubation and mechanical positive pressure respiratory assistance. This finding suggests that if for any reason the normal respiratory cycle is interrupted for a sufficient period, death may ensue even though the apneic period itself was insufficient to be life-threatening.

"DIVING"

We subjected 7 pigs to 30 seconds or one minute immersion of the nose and mouth in water as another form of obligate apnea. Blood pressure was elevated to a mean of 143 mg/hg during the dive from a control mean of 107 mm/hg and was accompanied by a marked reduction in heart rate from 200 to 130 beats per minute. If breathing resumed immediately on exposure to room air, blood pressure returned toward control levels as a transient tachycardia occurred. Hyperpnea also was present but subsided quickly. On the other hand, if breathing was not voluntarily reinstated, A-V dissociation and complete heart block were soon observed. Blood pressure fell with this low heart rate. This state was reversed by the first series of gasping inspiratory efforts resulting in tachycardia and hypertension. This sequence is strikingly similar to that seen in spontaneous apnea and nasal occlusion suggesting that a common event may sustain apnea once an adequate initial stimulus is provided or that the subsequent hypoxia may further suppress respiratory drive.

HYPOXIA

To determine the responses to hypoxia without apnea, we mechanically respired five animals with a mixture of 95 percent nitrogen and 5 percent carbon dioxide. Slight hypertension, bradycardia, some cardiac arrhythmias, enlargement of T waves, and ST segment changes were observed. After one or

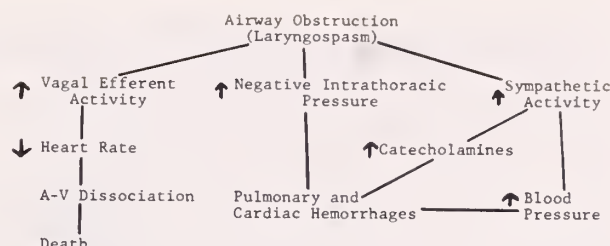


Fig. 1. Salient features include both vagal and sympathoadrenal discharges and a triple cause of observed cardiac and respiratory pathology. The observed pathology results most probably from a combination of coincident events including high negative intrathoracic pressure, and elevated arterial blood pressure and circulating catecholamines. Not included here is an indication of suppression or inhibition of the respiratory center which may occur subsequent to transient apnea.

two minutes of breathing nitrogen, the animals were returned to room air and removed from the respirator. Immediate voluntary resumption of breathing occurred and cardiac conduction disturbances were infrequently observed.

MECHANISMS OF PATHOLOGY IN SID

We would like now to direct attention to the post-mortem findings in human sudden infant death syndrome and note similarities and dissimilarities with those in the pigs used in this study. All animals were autopsied immediately after death. In babies, reports of pathology usually emphasize diffuse petechiae on all thoracic organs and pleura. Frothy mucous may or may not be found in the airways. Little other pathology has been noted.

The causative factor in the creation of the hemorrhages has been accepted as high negative intrathoracic pressure which we have also evidenced in the course of these experiments.

Post-mortem observations immediately after death (cardiac arrest) often showed the presence of laryngospasm (nearly occluded glottis), excess laryngeal and upper tracheal mucous, intrathoracic petechial hemorrhages on the pleura, lungs, thymus, and heart with a preponderance on the right ventricle. There were, in half the animals, massive transmural hemorrhages along the anterior septal-right ventricular margin. The internal surface of the ventricular chambers usually showed concentrations of subendocardial hemorrhages at the base of the heart and associated with the papillary muscle attachments. No hemorrhages were found in the kidney, mesentery, intestine, or liver.

BLOOD CATECHOLAMINES

This distribution of hemorrhages associated with a severe hypoxic stress suggests high levels of circulating catecholamines as an alternate or collaborate cause of the pathology. Accordingly, blood samples were drawn prior to and at one minute or two minutes of nasal occlusion for determination of catecholamine concentrations by a fluorimetric

technique. The results from six animals were that total catecholamine levels rose from a mean of 0.91 ug/l. plasma (0.00 to 1.92 ug/l range) to 14.38 ug/l. plasma after one minute of apnea (3.71 to 35.08 ug/l. range). Mean levels doubled to 29.5 ug/l. at two minutes of apnea. Catecholamine infusions producing similar blood levels to those achieved in these pigs produce subendocardial hemorrhages, principally on the left ventricle differing somewhat from the distribution observed in this study.

CONCLUSION

Figure 1 illustrates a hypothetical scheme including some events which we suspect may initiate the pattern of response to apnea in pigs. Interruption of the normal respiratory cycle, by whatever cause (spontaneous, nasal occlusion, or diving in this study) for a period of time exceeding 30 to 45 sec-

onds may prove fatal without itself being a life-threatening event.

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STATUS OF INTENSIVE RESPIRATORY CARE FOR ACUTE RESPIRATORY INSUFFICIENCY

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Initiation of Replication, Thermodynamic Considerations and Possible Mechanisms*

R. D. BLAKE**

ABSTRACT

Though many of the general features of gene expression have been outlined, numerous questions of considerable importance and detail remain. Virtually nothing is known, for example, about the mechanism required for initiating semiconservative replication of DNA. We can assume that complete access to the unique, hydrogen-bonded sections of the bases is required to achieve the highest degree of template specificity and fidelity and certainly no less to initiate gene expression. Consequently, we imagine two discrete mechanisms for base sequence recognition by enzymes of replication: 1) formation of a loop of j unpaired nucleotide residues, or 2) transient scission of one (or both) polynucleotide chains accompanied by unzipping of $j/2$ base-pairs. Calculations indicate that under the most favorable of conditions the spontaneous formation of a loop or bubble of j unpaired residues in DNA is extremely rare, occurring with a frequency of only once every $10^{j/2-3}$ base-pairs. The formation of such a loop at a specific "initiator" locus on the DNA while the latter is complexed with histones, Mg^{++} , polyamines, etc., as in chromosomes of eukaryotes, is very much less probable. This "inertness" of DNA convinces us that a particular mechanism is required to initiate replication (and possibly transcription) involving 1) a staggered, bilateral scission of both polynucleotide chains at a unique origin possessing two-fold rotation symmetry in its sequence (by an endonuclease), 2) unzipping of approximately ten base-pairs in both directions by "unwinding protein," 3) masking loss of bonding potential in the opposing chain with a surrogate poly- or oligonucleotide factor, 4) recognition of template initiator sequence of DNA by the polymerase complex, and 5) chain restitching with ligase.

The work I shall describe represents an attempt to second guess some of the high resolution molecular features of DNA replication during the earliest stages of this process. Succinctly stated our objective is to determine whether something can't be said about the precise way that the replication of DNA is or may be started.

We know a good deal now about replication as is summarized in Table 1. In a manner that was anticipated by Watson and Crick in their pioneering work on the structure of DNA, replication is known to be *semiconservative*, involving the unzipping of

TABLE 1

KORNBERG'S RULES OF REPLICATION*

1. Replication is semiconservative.
2. Replication is bidirectional.
3. Replication begins at unique points on the chromosome.
4. Replication of both strands of the helix proceeds by the addition of nucleotide monomers in the $5' \rightarrow 3'$ direction.
5. Replication occurs in short discontinuous pulses.
6. Replication is initiated by the production of a short segment of RNA to serve as a primer for DNA polymerase.

*After Kornberg, in "DNA Synthesis", Freeman & Co., Chapt. 7, 1974.

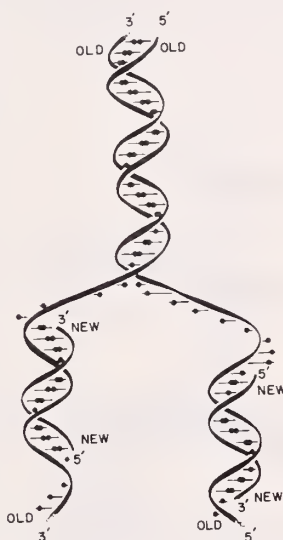


Fig. 1. The synthesis of replicate DNA using the original two strands as templates as proposed by Watson & Crick (*Nature*, 171, 737, 1953). This mechanism is termed semiconservative due to the fact that the original "old" helix, which splits apart to provide the template for the new strands, is partitioned so that the two helices that result after total replication contain one old and one new DNA strand.

parental DNA and copying of each strand as illustrated in Fig. 1. Replication is seen proceeding simultaneously on both strands, eventually to result in two daughter molecules with exactly the same primary structures as had the parent, consisting of one "old" and one "new" complementary strand. No detailed mechanism is intended by this figure. There are good reasons why the mechanism which seems implied should not be taken too literally.

As the second and third "rules" in Table 1 indicate, replication starts at a specific, unique point, called the "origin" in the DNA molecule and proceeds in both directions away from the origin along complementary chains. This is illustrated in Fig. 2a, showing an idealized version of one of Cairn's famous autoradiographic results, called theta structures, of an *E. coli* chromosome caught midway through replication. The growing bubble or eye is indicated by the heavier density of silver grains. Fig. 2b shows Cairn's interpretation of his result, an interpretation incidentally that everyone was

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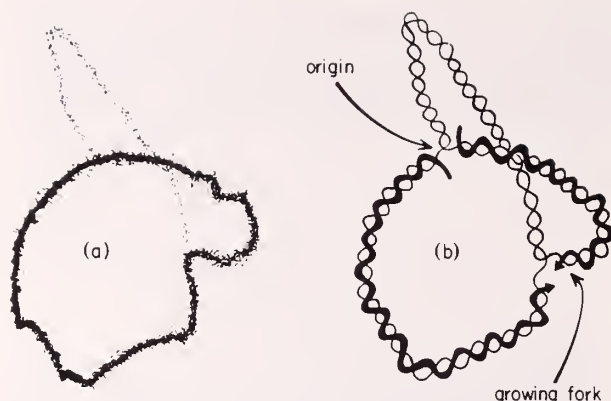


Fig. 2. Autoradiography of ^3H -thymidine labeled *circular* DNA from the *E. coli* bacterium during replication. (a) Idealized illustration of Cairns' original experiment showing a greater density of β tracks on the photographic emulsion along sections of the DNA undergoing replication. (After Cairns, *J. Mol. Biol.* 6, 208, 1963). The replicating DNA therefore would have a figure eight or "8" structure if it were opened up and flattened in two dimensions. (b) Mechanism of unidirectional, semi-conservative replication proposed by Cairns. The heavy-dark strand represents the growing "new" strand enriched in ^3H -thymidine.

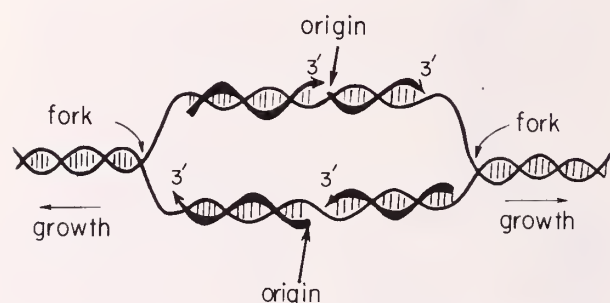


Fig. 3. Schematic illustration of semiconservative replication with growing forks running off in both directions from the "origin." Growth is $5' \rightarrow 3'$.

moderately happy with for almost ten years. When Cairns' mechanism is examined in greater detail, however, serious questions are raised. For example, when two twisted strands are pulled apart to form a loop, a large torque is generated in the intact sections that must eventually be alleviated. Also very recent results indicate that replication is *bi*-directional, moving off in both directions away from the origin. Thus, the origin should be placed at the apex of the growing loop rather than at one of the forks as suggested by Cairns.

The fourth rule in Table 1 indicates that replication of the new chain occurs *only* in a $5' \rightarrow 3'$ direction, as illustrated in Fig. 3. This means that the replication cannot take place on both chains simultaneously, but occurs $5' \rightarrow 3'$ away from the origin on opposite strands, but not $3' \rightarrow 5'$. The opposite parental chain is, therefore, single stranded as illustrated.

According to the fifth rule in Table 1, we note that replication takes place in short spurts, as illustrated in Fig. 4. Growth of new DNA chains takes place in pulses of between 100 to 1000 or so bases at a

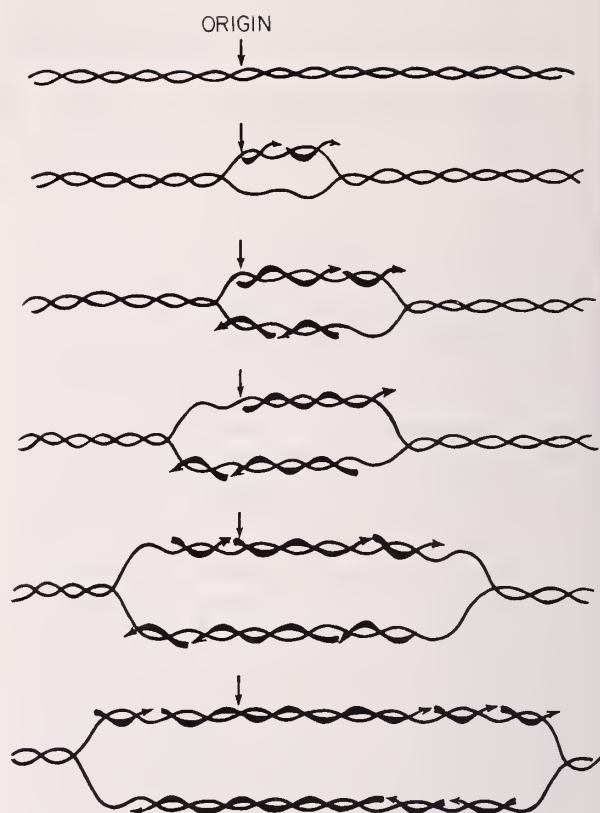


Fig. 4. Schematic illustrations of bidirectional replication. During the very earliest stages growth is imagined to occur discontinuously with the synthesis of short pieces of DNA ("Okazaki fragments") in a contiguous fashion along the template strand. These pieces, varying in length between 100-1000 nucleotide residues (depending on the organism), are later covalently linked together, presumably by a ligase enzyme.

time. These short sections of new DNA are then knitted together, represented in Fig. 4 by the longer arrows.

Finally we note that according to the sixth rule of replication, a new strand of DNA is initiated by the synthesis of a short piece of RNA which serves as a primer for the continuation of DNA synthesis. This is illustrated in Fig. 5. It has been demonstrated that a covalent link actually exists between the RNA primer and nascent DNA. The reason why the initiator primer must be RNA is somewhat of a mystery; however, we reason that it must have something to do with the fact that the hybrid RNA-DNA duplex will assume an A-DNA-like structure and that this structure will in all likelihood be perpetuated along the growing helix so long as that short piece of RNA is present. At some later stage this piece of RNA is clipped out and replaced with DNA, leaving the entire helix to then flip back into the normal B structure. The specificity of template and primer for the DNA polymerase III holo-enzyme may be distinguished from that of the, say, DNA polymerase I repair enzyme through such a mechanism.

The next Fig., 6, provides a visual summary of the various aspects of replication. It represents our cur-

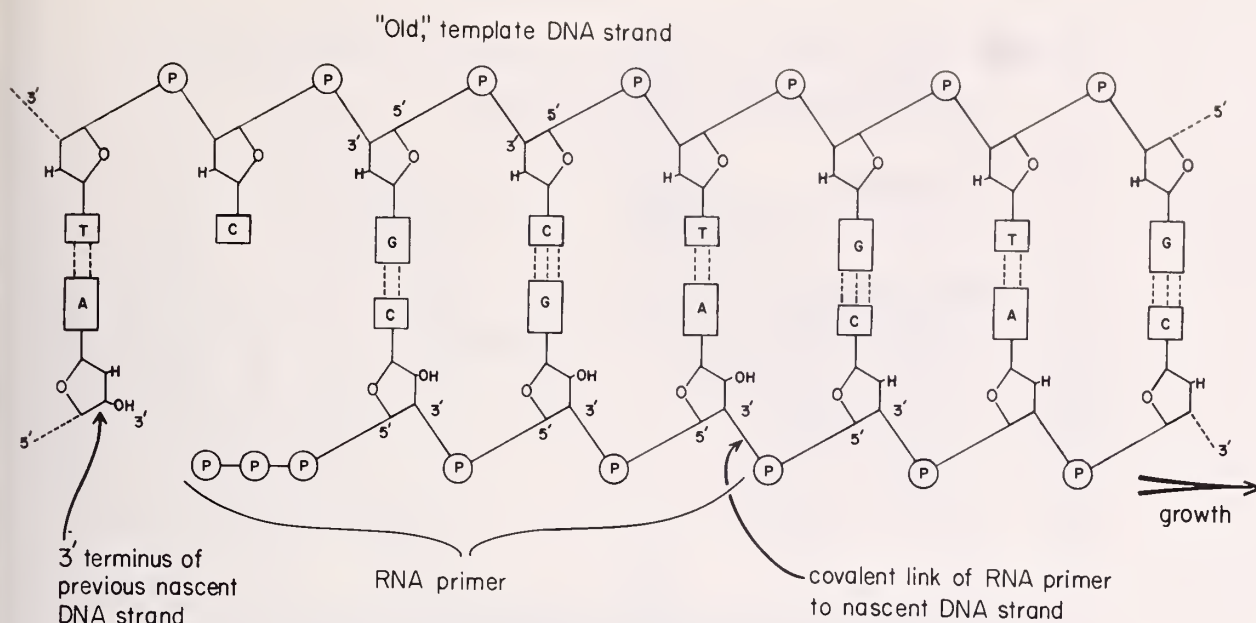


Fig. 5. Scheme for RNA-primed initiation of DNA synthesis.

rent understanding of this process and of the factors involved. Of necessity our description of replication has been almost purely phenomenological. We have said virtually nothing about important mechanistic details, that is, *how* these various steps occur, only that they do. Very little is known about these events at a detailed molecular level and so cannot be discussed with any authority.

Nevertheless, it is our objective to determine what factors might establish the place of origin of replication on the DNA and set this complex sequence of events into motion. The basic question as we see it is primarily a thermodynamic one. After a brief consideration of some thermodynamic factors we offer some speculation that, hopefully, may provide the right sort of tactical basis for filling in some answers to those very difficult questions that remain, and that, for a variety of reasons, are not likely to be forthcoming by the same kind of approach that contributed so much of what we now know about replication.

In the consideration of plausible models for replication, the first question that we face concerns the nature of the process required for recognition of a unique origin on the DNA. Most models assume that unpairing of a particular contiguous sequence of bases, say 5 to 10 or 12 bases, whatever is needed to accommodate an enzyme, must be unpaired. If we estimate the average globular enzyme as being roughly 35Å in diameter, for example, then we must think of a loop of about 10 base residues. For reasons that will become evident below, this assumption of a loop is made with the greatest reluctance.

Unpairing is required so that the most distinctive features of the nucleotide can be exposed. Such features are normally sequestered through hydrogen bonding and stacking interactions. It is not unreasonable to expect, therefore, that the best way to

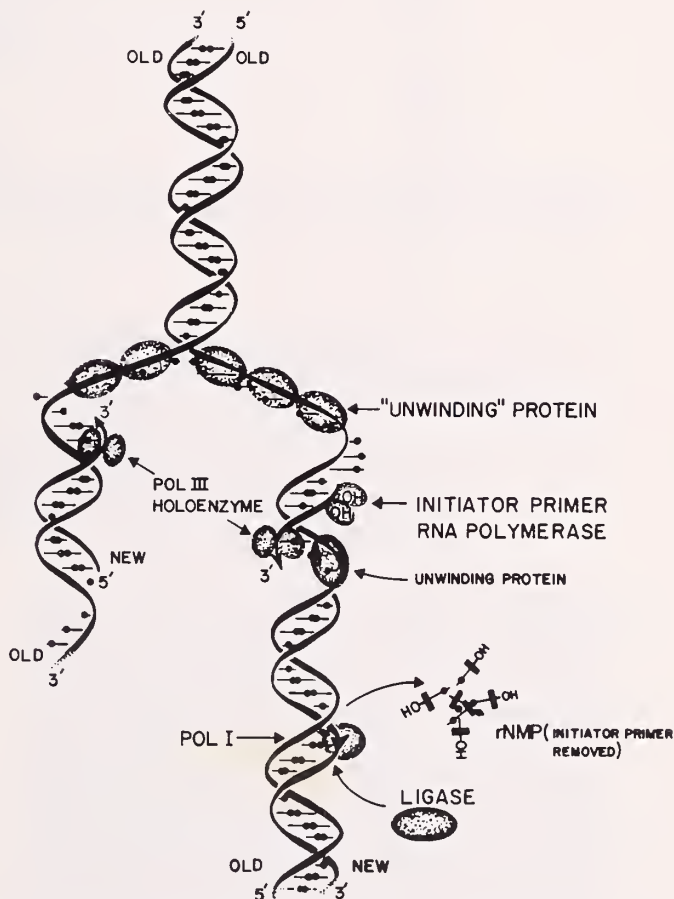


Fig. 6. Summary of the various events and factors known or suspected to occur during replication.

achieve a very high level of specificity between base sequence and enzyme is to unpair and unstack the base residue, thereby exposing as much of the base as possible. The base-pair seen edge-on as it is in the

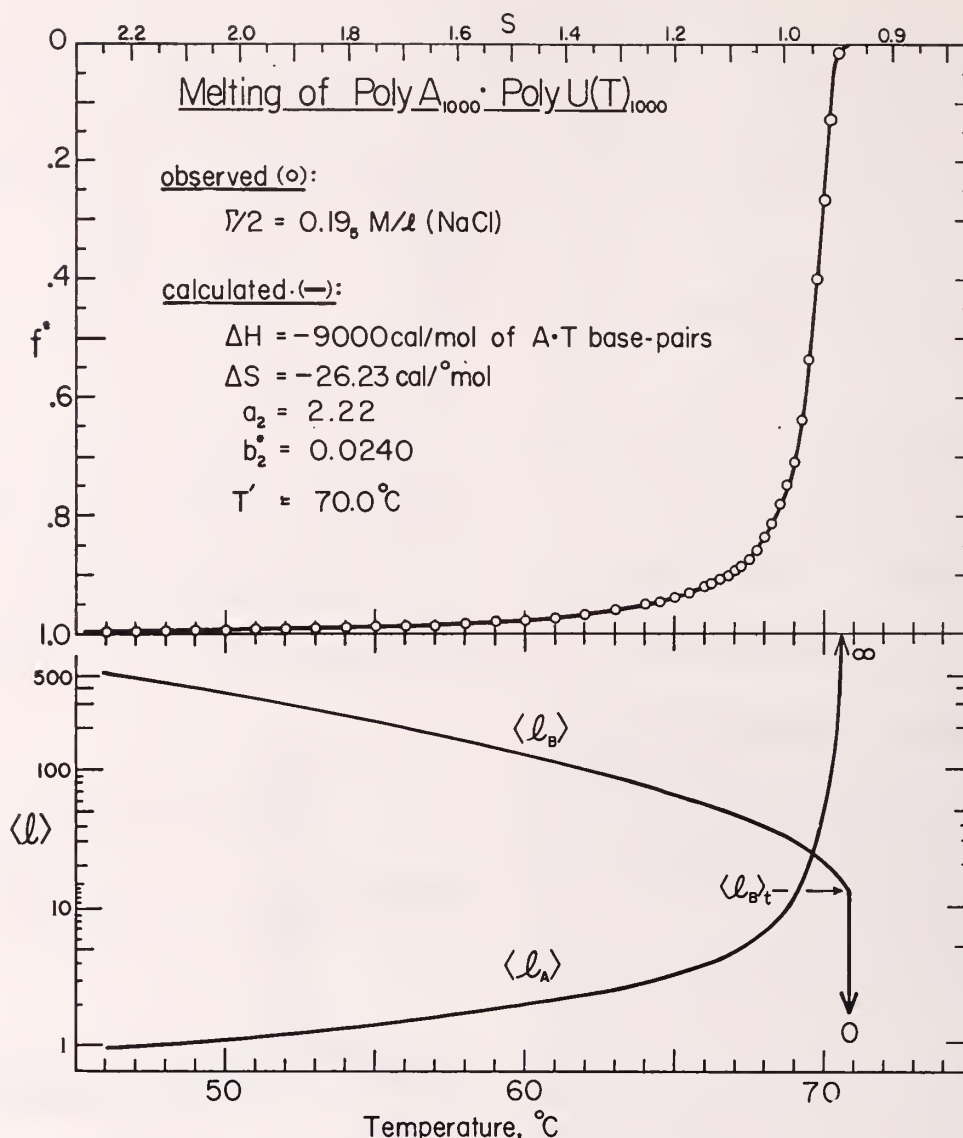


Fig. 7. The upper sigmoidal curve represents a comparison of observed (open circles) with calculated (solid line) melting curves of poly(A-U) according to the scheme illustrated in Fig. 8, using values for the various parameters given in the upper left. T_t is the phase transition temperature, while other terms are self-explanatory or defined in Fig. 8 or Table 2.

helix seems rather featureless. Of course, as everyone agrees, complete accessibility to the hydrogen bonding potential of the nucleotide residues in DNA is an *eventual* requirement for semiconservative replication in any case; nevertheless, the assumption that the exposure of nucleotides must involve the formation of a loop in the DNA helix as the *initial event* will not draw unanimous approval. Indeed, recognition of a unique sequence in the DNA at the "origin" can probably be made just as well without forming a loop. For precedents we might cite the sequence specific binding of restriction enzymes and of the lac repressor protein. Even such simple compounds as actinomycin D and netropsin are able to bind specifically to G-C and A-T base-pairs, respectively, (albeit through intercalation in the case of actinomycin D). Though very few discussions that I know of have focused direct-

ly on this question of initiation of replication, one is left with the feeling from the various macroscopic models that the enzymatic processes involving base sequence specificity in DNA involve the formation of a complex between enzyme and the unpaired nucleotide residue, and that unpairing is a spontaneous event. I would say categorically that it is not. Our statistical thermodynamical studies on the behavior of model synthetic DNAs indicate that the spontaneous formation of an unpaired loop segment in the DNA helix is an extremely unlikely event, and all the more so if we must produce that loop at a unique locus in the molecule, such as at the origin.

Fig. 7 illustrates the type of experiment that we have used to determine the frequency of unpaired bases in the DNA molecule. Attention should be focused, for the moment, to just the sigmoidal melting curve in the upper half of this figure, the plot of

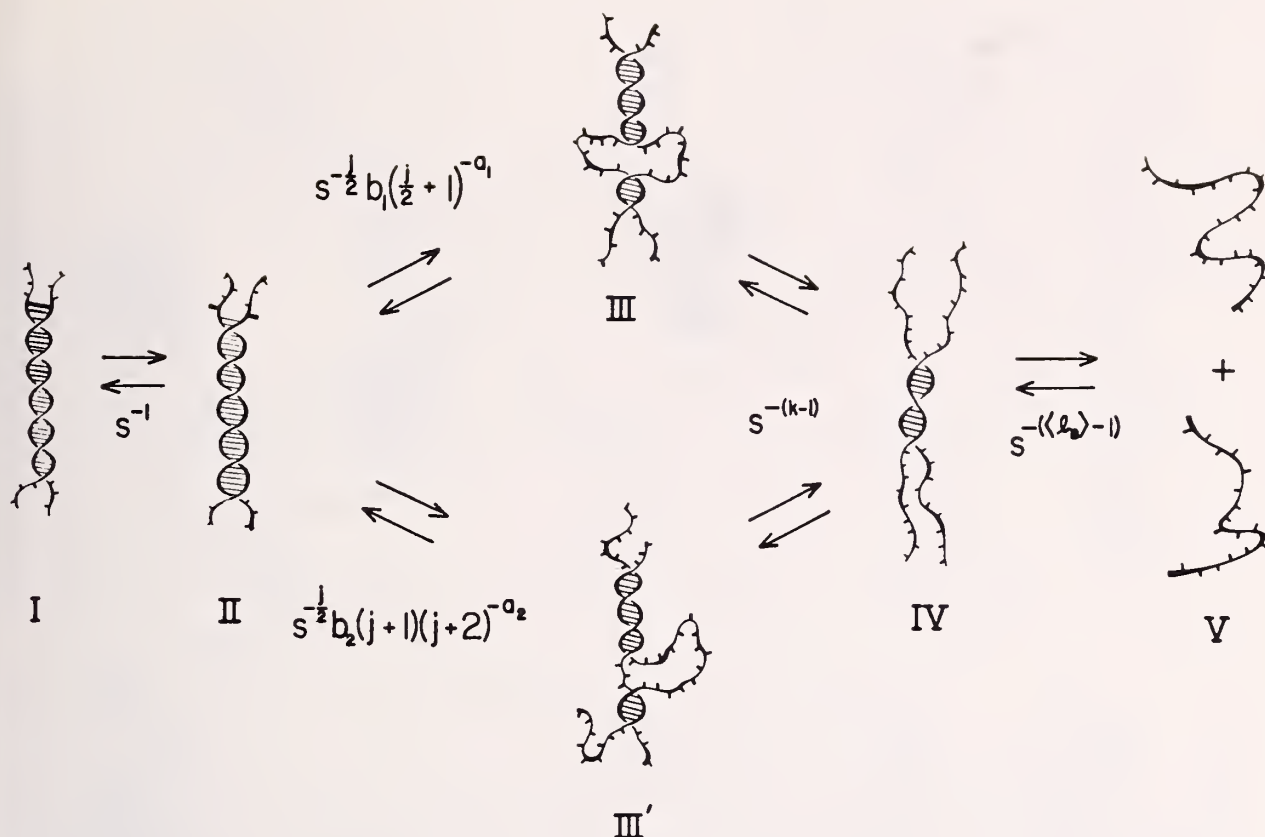


Fig. 8. Scheme for melting of polynucleotides. Analysis assumes polynucleotide chains to be effectively of infinite length, and that loops form either in a matched fashion, i.e., via III, or in a mismatched fashion (III'). Parameters for various equilibria are defined in Table 2.

f , fraction of bases in the helical state versus temperature. The open circles represent the observed melting of a synthetic double helix composed of one strand of polyadenine or poly A and the other of poly U. There are several reasons why we chose to examine this particular helix rather than DNA itself. The most important reason is that the analysis of the melting of DNA is extremely complicated. In fact, the number of parameters is more than is needed to describe the proverbial elephant. At least three parameters are needed to describe the behavior of just one nearest neighbor base-pair sequence. In DNA there are 12 different neighbors while our model system has only one, A-U upon A-U. Another reason for choosing the A-U system is that this pair is among the weakest of the 12 nearest neighbor sequences found in DNA and so it represents a model system that is most favorable for ready loop formation, the mechanism we appear to be challenging. There are several other reasons for choosing the A-U system, but essentially they all favor a less complicated analysis. Incidentally, this melting curve was carried out under solvent conditions that closely simulate those in the cell.

Before considering the theoretical melting curve for this primitive DNA-like helix, which is given by the solid line in this figure, 7, I would first like to run quickly through the model system upon which the analysis is based; shown in Fig. 8. According to the traditional formalism for the various processes

TABLE 2

DEFINITIONS OF SOME OF THE PARAMETERS USED TO DESCRIBE THE MELTING OF HELICAL POLYNUCLEOTIDES.

S ,	"STABILITY" OR "PROPAGATION CONSTANT," THE EQUILIBRIUM CONSTANT FOR FORMATION OF A BASE-PAIR NEXT TO AN ADJACENT BASE-PAIR.
b ,	"STACKING PARAMETER," RELATED TO THE FREE ENERGY OF STACKING A BASE-PAIR ON AN ADJACENT BASE-PAIR: $b = \mu \exp(\Delta G_{st}/RT)$
a ,	"LOOP CLOSURE EXPONENT"
j ,	NUMBER OF NONBONDED RESIDUE PAIRS IN A DISORDERED LOOP SEGMENT.
$\langle \ell_B \rangle$	MEAN HELIX LENGTH (BASE-PAIRS)
$\langle \ell_A \rangle$	MEAN LOOP SIZE (RESIDUE PAIRS)
SUBSCRIPTS:	
1,2,	NUMERAL SUBSCRIPTS DISTINGUISH a AND b FOR THE VARIOUS MODELS, <u>1</u> FOR EVEN OR MATCHED LOOPS AND <u>2</u> FOR MISMATCHED LOOPS.
t ,	VALUE OF THE PARAMETER SUBSCRIBED AT THE PHASE TRANSITION TEMPERATURE.

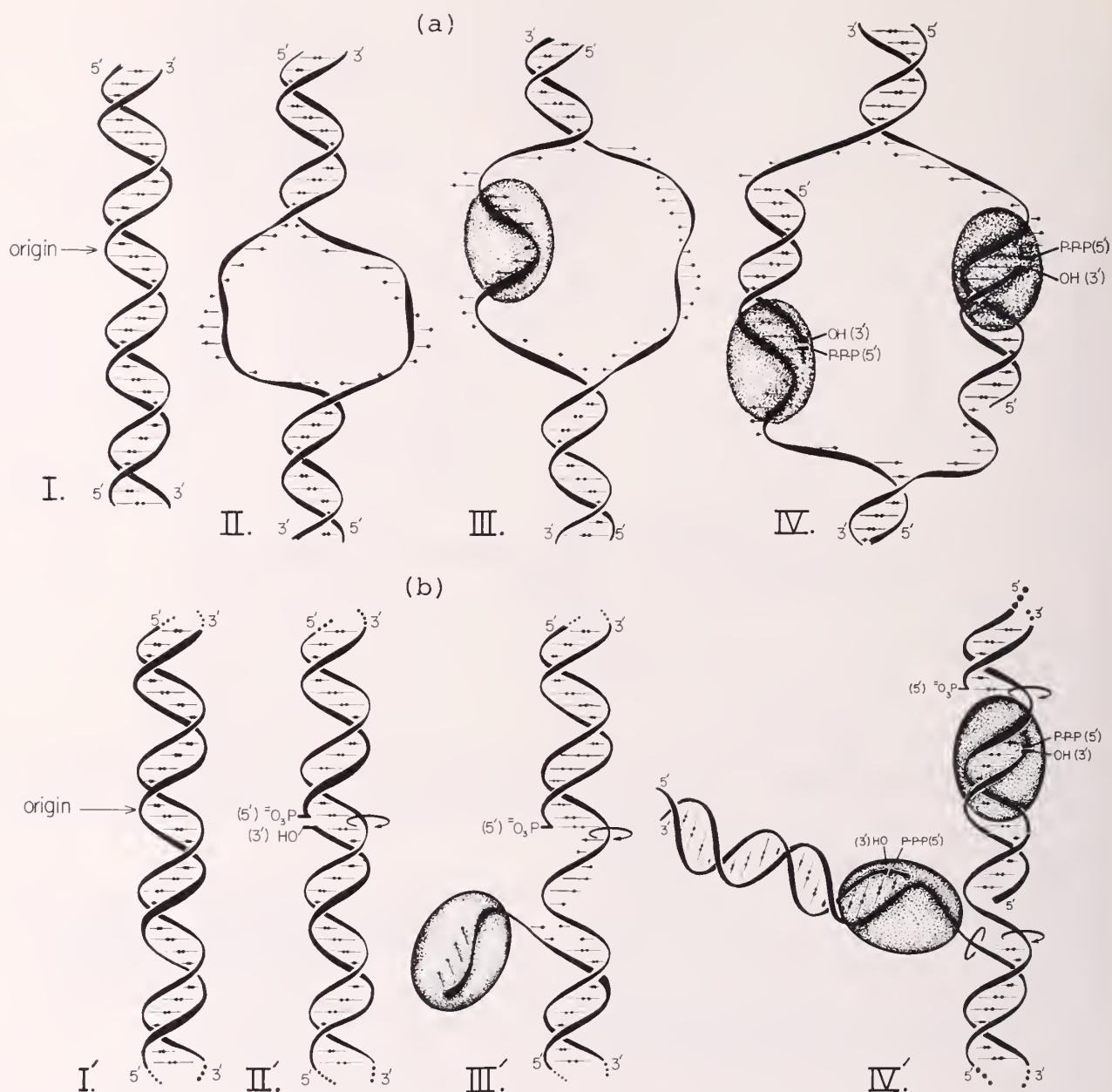


Fig. 9. Models for the initiation of semiconservative replication. (a) In this model replication begins with the formation of a loop at the origin (structure II), thereby exposing a particular sequence of bases to which DNA-Initiator-RNA-polymerase binds (III) perhaps in the presence of a special subunit protein with properties analogous to those of sigma factor in transcription. (b) Replication begins with a nick in one strand of the helix (II'). The involvement of an endonuclease with the capability of recognizing the "origin" is, therefore, the initial event in this model.

seen in this figure, the equilibrium constant for formation of a base-pair at the end of a helical segment is called the stability constant and is denoted by S . This equilibrium is represented by that between the helix labeled I and II in this figure. As melting progresses, small bubbles or loops begin to develop and grow in size as the double helix begins to weaken. In the case of DNA the loops are symmetrical, that is, the number of unpaired, dissociated residues in the two complementary chains must be equal. Thus, we imagine melting to take the upper route in this figure, through the structure labeled III. Our model synthetic DNA is not

restricted to symmetrical or matched loops, however, and can take the lower route through structure III' in which loops can form with equal probability with regard to size in either chain. The corresponding equilibrium expressions for these two events indicate the presence of two additional parameters: b the so-called "stacking parameter," and a the "loop closure exponent." j in this figure simply refers to the number of nonbonded residues in the loop. We would intuitively expect the equilibrium constant for loop formation to be proportional to the size of the loop.

Table 2 summarizes some of the more critical de-

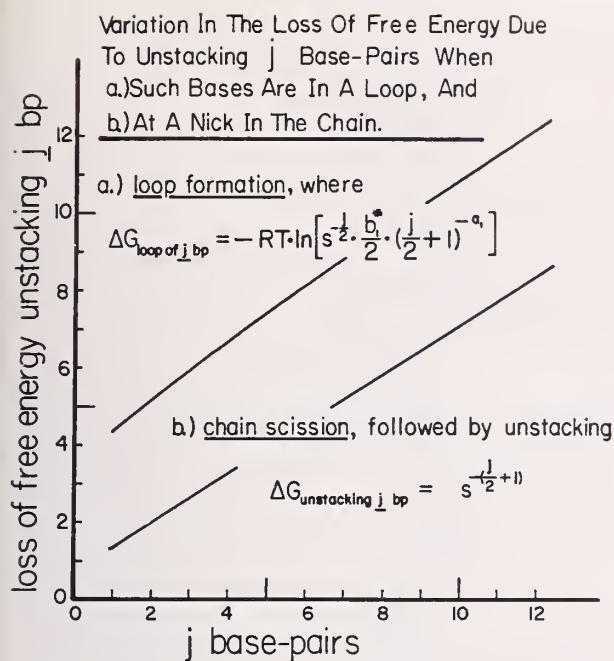


Fig. 10. Variation of ΔG for dissociation of j base-pairs for the two models illustrated in Fig. 9.

definitions associated with the theoretical analysis of melting. The first three are parametric constants that can be evaluated or refined semiempirically by fitting theoretical with observed melting curves. Once a good fit has been obtained we can then use these parameters to evaluate the mean helix length, $\langle l_B \rangle$, and mean loop size, $\langle l_A \rangle$, our final objective. Details of the computations can be found in the literature [Blake, *Biophys. Chem.* 1, 24 (1973)].

We can now return to the melting curve in Fig. 7. As one can readily imagine the greatest sensitivity in the fitting process is obtained in the region of greatest change in melting, therefore the actual analysis is made with precision data limited to the two or so degrees bracketing 95% of melting ($\sim 68-70^\circ\text{C}$). The theoretical curve giving the best fit, and represented by the solid line in this figure, was calculated with values for various parameters given in the upper left-hand corner of Fig. 7. Without going further into the analysis, suffice it to say that these values are in very good agreement with theoretically expected values. This gives us greater assurance in calculating the dependence of mean helix, $\langle l_B \rangle$, and loop, $\langle l_A \rangle$, sizes with temperature, shown in the lower half of this figure. The relevant consequence of the dependence of the latter two parameters on temperature are seen at the lower temperatures where the frequency of loops in this synthetic helix approaches *one looped out base-pair for every helical segment of 500 base-pairs*. At physiological temperatures and below the probability of encountering a looped out base-pair is 1 in well over 1000; consequently, if we require a loop of, say, *six* base-pairs the frequency is only 1 in one billion, clearly a very unlikely event and all the more so if we

DIFFERENCE BETWEEN THE FREE ENERGY FOR UNSTACKING j BASE-PAIRS IN A LOOP; AND ADJACENT TO A NICK IN ONE CHAIN OF THE DNA DUPLEX ($\Delta G_{\text{LOOP}} - \Delta G_{\text{NICK}}$).

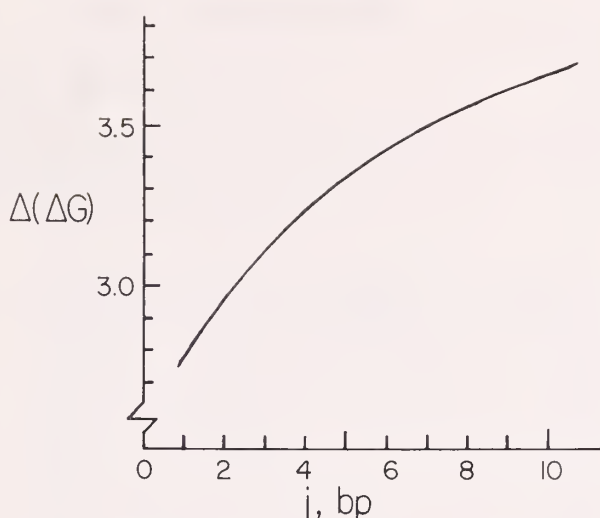


Fig. 11. The difference in free energy for initiating replication by the two models in Fig. 9.

insist that the loop occur at a unique locus. A number of other factors, for example, the increased torque generated in the helical segments of DNA, or the presence of the more tightly bound G-C base-pairs, etc., all conspire to reduce the probability of loop formation. The conclusion is then that DNA is a remarkably inert molecule.

Compared to proteins, particularly globular proteins, DNA has a very simple structure and lacks any catalytic role that we know of. Consequently, we cannot expect this molecule to serve its function in any other manner than as a simple data bank or library of genetic information for the cell. Thus, we see DNA passively awaiting withdrawal of information through interaction with specific proteins. How then is the first loop made in the DNA? This brings to mind the old cart and horse identity question. If there is no loop, how is the sequence at the origin recognized? Alternatively if the origin is not recognized, how can a loop be formed?

There are two possibilities. Fig. 9a illustrates the first of these. A small loop is first formed in the DNA at the origin allowing the initiator sequence to be recognized by an RNA polymerase as in structure III and IV. We still face those difficult questions of how the loop is generated and torque relieved.

The second possibility is illustrated in Fig. 9b. Here an endonuclease is imagined to put a nick in one strand which more-or-less eliminates the torque problem since now we have free rotation of the chain without forcing it to unravel. Also the nicked strand can unzipper permitting complete accessibility to the base sequence normally sequestered in the helix. Thermodynamically this is much more favorable than forming a loop as we see in Figure 10.

Blood Clots Labeled With Powdered Tantalum for Experimental Pulmonary Emboli*

E. CONVERSE PEIRCE, 2ND, M.D., DANIEL J. KRELLNSTEIN, M.D., Ph.D. and CHRISTOPHER W. BRYAN-BROWN, M.D.**

ABSTRACT

Interest in the pathophysiology, course, and treatment of pulmonary embolic disease has prompted us to develop a more satisfactory radiopaque label for experimental pulmonary emboli. Blood clots prepared with barium sulfate (the most used label) are poor in quality, being soft and friable and with a non-uniform label. Tantalum was selected because it is nearly ten times as radiopaque weight for weight as barium sulfate and has been used effectively to outline the tracheo-bronchial tree. 1.5 gm of tantalum (1 and 5 micron diameter powder) was suspended in 2.5 ml of thromboplastin (Fibro-Plastin[™]), rapidly mixed with 50 ml fresh homologous dog blood, and immediately transferred to a Petri dish. 1.5 hours later the clot was cut into 16 pie shaped pieces with a scalpel and refrigerated. After overnight clot retraction, the plasma was decanted and the clots transferred to a Toomey catheter tipped syringe. Clots were injected through a 1/4" ID femoral cannula in chlorolose anesthetized dogs. The 5 micron tantalum mixed poorly and was used only a few times. The 1 micron tantalum produced uniform clots of high quality that were easy to handle. 1 ml per kg provided a reliable LD 100 dose. Distribution of clots was quite uniform within the pulmonary artery and could be documented very satisfactorily radiologically. The 1 micron tantalum did not interfere with routine histologic sections. The method has been very helpful in randomized studies using extracorporeal membrane oxygenation (ECMO) to support baboons after massive pulmonary embolism.

INTRODUCTION

Use of radiopaque tagging of clots for experimental studies of pulmonary embolization has been found helpful by many investigators.^{1,2,6,8,10} The usual tags, barium sulfate, or organic iodides have produced clots of poor quality that are generally soft and friable and with non-uniform radio density. Geelhoed, et al in excellent recent studies using extracorporeal membrane oxygenation (ECMO) to support baboons after massive pulmonary emboli-

zation elected not to use a clot label.⁷ Instead they used serial angiograms to follow the position and resolution of the emboli. We have carried out similar studies in dogs using radiopaque labeling of mature clots. Animals were treated on a random basis with ECMO after receiving massive emboli. Barium sulfate labeled clots were tried first and found to be unsatisfactory. We then experimented with two forms of powdered tantalum as a label. This material is nearly ten times as radiopaque, weight for weight, as barium sulfate and has been used very successfully in recent years for bronchography.⁹

MATERIALS AND METHODS

Barium sulfate, 40 to 60% of final clot volume, was thoroughly mixed with 10 ml of fresh blood to which was added 0.5 ml thromboplastin (Fibro-Plastin[™]). Clots were stored in 0.25 inch ID polyvinyl tubing, and subsequently injected intravenously in amounts averaging 1.5 ml per kg in large chlorolose anesthetized mongrel dogs to produce massive pulmonary embolization.

Tantalum powder† (1.5 grams of 1 micron and 5 micron diameter) was suspended in 2.5 ml of thromboplastin in a 100 ml plastic beaker by rapid circular mixing. Fifty ml of homologous dog blood drawn freshly less than 30 seconds before into a plastic syringe was rapidly added to the tantalum suspension and the mixture immediately transferred to a 9 cm Petri dish. 1.5 hours later the clot was cut into about 16 pieces with a scalpel and placed in an ordinary domestic refrigerator. After overnight retraction, serum was decanted and the clots were transferred to a plastic Toomey catheter tipped syringe. They were injected through a 0.25 inch ID polyvinyl tube, in a manner similar to the barium sulfate clots, in amounts of 1 to 2 ml per kg.

The carefully monitored dogs had been prepared prior to the clot injection for immediate ECMO. They received ECMO by the veno-arterial perfusion mode for 4 hours on a random basis. The control dogs received standard resuscitative and supportive measures. The position of the clots was followed by antero-posterior and lateral chest radiographs. Postmortem examinations included histologic studies.

*Presented at the First Annual Maine Biomedical Science Symposium, Augusta Civic Center, March 14-15, 1975.

**Departments of Surgery and Anesthesiology, Veterans Administration Hospital, Bronx, New York and Mt. Sinai School of Medicine of the City University of New York.

V.A. Project #7240-06. Supported also by National Heart Lung Institute Contract No. 1-HR-42923.

†Fansteel Metals, #1 Tantalum Place, North Chicago, Illinois.

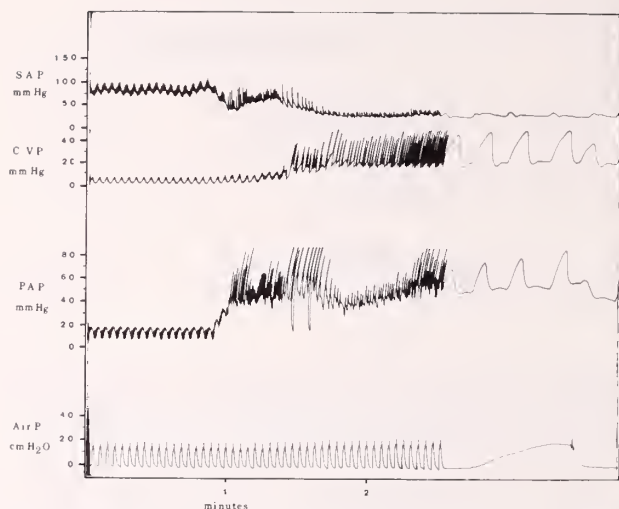


Fig. 1. Dynamic effects of injection of 1 ml per kg of tantalum labeled homologous clot are shown. There is an abrupt rise in the pulmonary artery pressure (PAP). Within 1 min. this has reached a systolic level of 80 mm Hg. At the same time, the systemic arterial pressure (SAP) starts to fall. After a partial stabilization, there is a bradycardia and the pressure declines to 45/30 mm Hg. The central venous pressure (CVP) rises slightly after a brief delay but a few seconds later tricuspid regurgitation occurs producing a pulse not very different from that of the pulmonary artery. The airway pressure trace (Air P) shows that the pulmonary hypertension is accompanied by a loss of compliance. The lung becomes stiffer with a rise in peak pressure from about 15 to 20 cm H₂O with no change in inflation volume.

RESULTS

The barium clots varied greatly in the degree of clot retraction and were very friable. Radiopacity within the clots was distributed in a non-uniform manner. Clots tended to fragment on injection and to distribute unpredictably in the pulmonary tree. The cardiopulmonary effects of a given dose seemed quite variable.

The 5 micron diameter tantalum powder could not be maintained in suspension. Attempts to get uniform mixing only caused defibrination of the blood. Clots of good quality could be produced but the tantalum was never uniformly distributed. This size was used only a few times.

The 1 micron diameter tantalum powder handled easily once the basic mixing steps had been learned well. Distribution of tantalum was remarkably uniform in the clots which were plastic in quality but very strong. Clots readily molded to the tubing shape and did not appear to fragment within the pulmonary vascular tree. One ml per kg was found to be a reasonably reliable LD 100 dose, animals generally dying within 10 to 15 minutes after injection despite resuscitative and support efforts.

	Pulmonary Emboli Tantalum Labeled Homologous blood - 1 ml / kg	
	Lived*	Died
CONTROL	1	7
ECMO	6	1

*Beyond end of perfusion

Figure 1 shows typical changes in some of the moni-

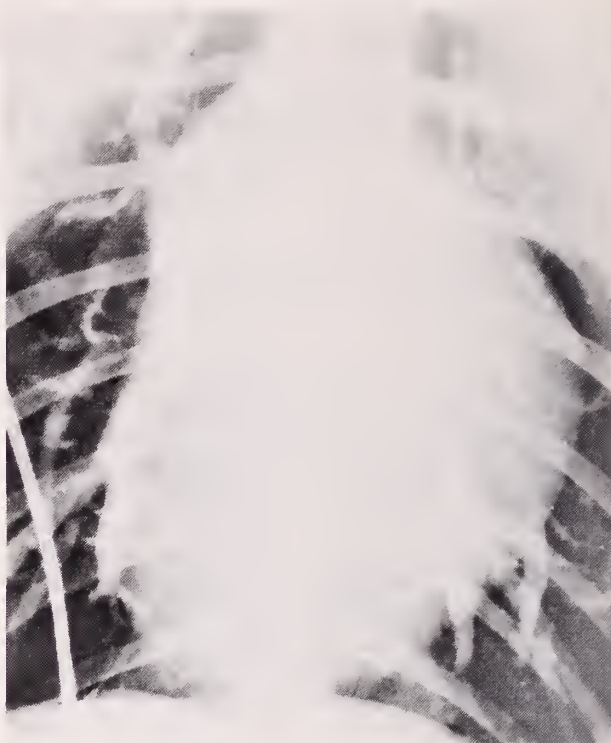


Fig. 2. The radiographic appearance (in antero posterior view) after injection of 1 ml per kg of tantalum labeled homologous clot is shown. Lobar and some smaller pulmonary arteries are rather uniformly filled with emboli. The position of the clots generally shows no definite change during 4 hours of perfusion though the condition of the subject improves markedly.

tored respiratory and circulatory variables immediately following the clot injection. The uniform clot distribution (Figure 2) did not appear to change with four hours of ECMO support. Nevertheless, there was marked improvement in vital signs and a striking reduction in the pulmonary artery hypertension. Good quality histologic sections could be prepared without difficulty from the injected lung.

DISCUSSION

Massive pulmonary embolization is still an important cause of sudden death despite the availability of new sensitive tests for intravascular clotting (e.g., scanning after the administration of ¹²⁵I-Fibrinogen¹¹), ready availability of prophylactic anticoagulant drugs, and more effective methods of treatment including cardiopulmonary bypass with embolectomy.³ Serial angiographic studies in clinical cases have suggested that the usual fate of pulmonary emboli is lysis with re-opening of blood vessels.⁵ Studies with various fibrinolytic agents have been confirmatory of this resolution of pathology.¹² More recently perfusion, using ECMO for a limited period of support, has shown considerable promise.⁷ It appears that patients who do not die soon after the embolization of overwhelming pulmonary and circulatory failure have a greatly improved chance of discovery.¹² Especially needed to gain a better understanding of the natural history of the

embolic process are: a) information relating the distribution of emboli to the dynamic cardiopulmonary changes, b) any alterations in clot distribution to be found during the period of rapid amelioration of shock, and c) the final fate of the clots. All of these questions may be better answered with the use of well labeled clots that are similar to natural ones and have reproducible physical characteristics.

Tantalum is a very superior label for both acute and chronic studies of pulmonary emboli because it is non-reactive and very radiopaque. This means that relatively small quantities are required and that little or no alteration in the character of the clots is likely. Surface coating of clots with tantalum has been reported by Austin, et al.² They have used 5 micron tantalum powder and have followed the fate of pulmonary emboli by serial radiographs. Preparation of histologic sections has been possible using a bone knife. Surface coating requires that the tantalum be sprayed from an atomizer, a procedure that entails the remote danger of flash ignition of the tantalum powder.⁹ Experiments with tantalum in human bronchography have shown it to be inert. No chronic pulmonary changes could be detected though some of the tantalum was engulfed by macrophages.⁹ Carroll, et al have reported permanent tagging of the wall of the pulmonary artery with injected tantalum powder⁴ while Austin, et al have some evidence that intraluminal tantalum may become incorporated in organized thrombus.² It, therefore, seems premature to suggest that tantalum

is a suitable material for clinical studies of labeled emboli.

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INITIATION OF REPLICATION, THERMODYNAMIC CONSIDERATIONS AND POSSIBLE MECHANISMS

Continued from Page 104

question. The mechanism involves a particular kind of bilateral cleavage of the DNA at the place of origin; with the nick in each chain being staggered at the two ends of a sequence of base-pairs having

two-fold symmetry. Finally, the model obviously predicts the existence of an enzyme with these properties; which are not that different from so-called restriction enzymes.

Reminder to M.M.A. Members

CONTINUING MEDICAL EDUCATION ACTIVITY REPORT

The bylaws of the Maine Medical Association were amended in June of 1973 as follows: Chapter I, Section 11, — "Each member of the Maine Medical Association shall be required to report his activities in continuing medical education every year according to a format provided by the Committee on Continuing Medical Education."

Only active, dues-paying members are required to report this year.

Please fill in your activity report promptly and return to the M.M.A. office, P.O. Box 250, Brunswick, Maine 04011.

Clinical Engineering

A Potential Resource of Engineering Services†

W. PAGE C. CLASON, M.D.* and E. M. SHEPPARD, Ph.D.**

The rapid growth of technology in medical science since 1950 has created many problems for both clinicians and researchers. In general, research personnel are more involved with basic technology. At times, basic research is aimed at solving technological problems. Problems involving technology stand in the way of progress of basic research more often than not. In clinical practice, physicians usually delegate technological problems for solution. In the community hospital, especially in a rural state, technological problems frequently are delegated to the nursing service or to the hospital maintenance and engineering service. Usually these services are not equipped to deal with these problems for many reasons. Time is usually assigned to other tasks on a full-time basis and frequently there is lack of expertise and/or necessary equipment to cope with the specialized engineering problems produced by modern technology.

The Clinical Engineering Laboratory at the University of Maine was established in 1972 in an attempt to provide a basic engineering resource for hospitals throughout the State of Maine. The Laboratory itself is located in the basement of Barrows Hall in the Department of Electrical Engineering at Orono, Maine. There is also an office in Portland, Maine and an office at the Eastern Maine Medical Center in Bangor. The core staff includes a team of personnel including a physician, a professor of electrical engineering, two practicing engineers, a registered nurse, three special electronics technicians, a graduate student, five undergraduate students, and a secretary. Members of this team have had extensive experience in dealing with problems concerning the management of modern medical technology in twelve hospitals in the State of Maine. These hospitals are the Augusta General Hospital, Calais Regional Hospital, Cary Memorial Hospital in Caribou, Central Maine General Hospital and St. Mary's Hospital in Lewiston, Down East Community Hospital in Machias, Mercy Hospital in Portland, Millinocket Community Hospital, Penobscot Bay Medical Center in Rockport, Rumford

Community Hospital, Westbrook Community Hospital and Eastern Maine Medical Center in Bangor. The team has had the greatest experience in the management of technology concerned with cardiac, respiratory and renal physiology; however, it has been involved in many other areas of engineering including corrosion of pipes, regulation of air conditioning systems, treatment of sick trees and the design of critical care and intensive care units.

The basic concept behind the development of the Clinical Engineering Laboratory is to provide for shared biomedical engineering services in a rural state where such services could not be provided because of the lack of the critical mass needed to provide support of full-time personnel. In theory, if such a service were available, it could be purchased on a part-time basis by facilities which could not afford or did not need full-time engineering services. Locating the Laboratory within the University framework allows the resources of the University to be brought to bear upon community problems and avoids the necessity of costly reproduction of specialized measurement equipment, testing and calibration apparatus and specialized expertise in the application of this equipment. The program emphasis lies upon training hospital personnel to be as fully self-sufficient and self-supporting as possible while allowing for provision of back-up services in engineering which could not otherwise be made available. The intent of the Laboratory is to provide for engineering support to community hospitals on a not for profit basis and to be fully self-supporting within two years. The program has received support from the Maine Heart Association, Maine's Regional Medical Program, and more recently it has received substantial support from the W. K. Kellogg Foundation. The primary thrust of this latter support has been to provide for shared engineering services in conjunction with the Universities of Vermont and New Hampshire.

The Clinical Engineering Laboratory at Orono has an electronics maintenance shop, a physiological blood gas laboratory, and a blood gas calibration laboratory. It has both the equipment and expertise for calibrating inhalation therapy equipment and hospital gas distribution systems. It has transmission facilities available which are suitable for dealing with problems of management of cardiac monitoring equipment on a remote basis. It is currently planned to establish a mock clinical chemistry laboratory and a mock intensive care area to allow for specialized training of personnel in the management, maintenance, and repair of the asso-

† Presented at the First Annual Maine Biomedical Science Symposium, Augusta Civic Center, March 14-15, 1975.

* Medical Director, Critical Care Unit, Eastern Maine Medical Center, and Lecturer, E.E. Department, University of Maine at Orono.

** Director of Clinical Engineering Laboratory and Professor of Electrical Engineering University of Maine at Orono. Consultant in engineering at Eastern Maine Medical Center.

This program is supported in part by a grant from the W. K. Kellogg Foundation.

ciated technology outside of the hospital environment.

Management of medical technology implies making technology work in practice in the hands of medical personnel in the field, in order to attain the purpose for which the technology was intended, both in patient care and in research applications. The primary thrust of the program is educational and not aimed at the basic research and/or clinical application itself except in so far as knowledge of these applications is essential to the management of technology. The approach to this management problem has been multifaceted and modular in nature so that it can be tailored to the specific unique needs of a small rural hospital in a meaningful fashion. It might be helpful to review some of those modules as they have been developed over the past two years in actual practice.

1. Functional Testing — The Laboratory is prepared to provide for both periodic and sporadic evaluation of specific items of medical equipment to assure their proper function in three areas: 1) suitability of application of use intended, 2) suitability in regards to safety and regulatory codes, and 3) suitability in regards to manufacturer's specifications and/or design specifications.
2. Repair and Maintenance — The Laboratory is in a position to provide for routine preventative maintenance on specified equipment if this cannot be handled by hospital personnel. The laboratory is also prepared to provide for emergency on-call repair service of specified critical equipment.
3. Purchase Consultation and Evaluation — The Laboratory is in a position to provide for purchase evaluation and advice regarding purchase of new equipment particularly in the area of specialized applications of the technology. The laboratory is also prepared to provide for functional testing of equipment prior to its being put into service. This testing can be done either at the local facility or at the University in Orono.
4. Education — Provision has been made for seminars concerning specialized technology, both in terms of theory and application, to be provided within the local facility. Seminars are given regularly at Orono and, on occasions, at other locations throughout the University of Maine system which are specially tailored to the demands which have been made upon the laboratory. Regular scheduled seminars have involved hospital engineering and maintenance personnel. It is proposed to start programs which will involve purchasing agents of hospitals. The Clinical Engineering Laboratory has both a two-year and a four-year program for the purpose of training undergraduate students in the management of technology in the hospital environment. At present, nine

students are enrolled in this program. The purpose of this program is to supply specialized technicians who have had unique training for the biomedical field in the community hospital. There is also a master's program which is capable of providing advanced training in the management of cardio respiratory physiology and/or specialized technological equipment.

5. Training — The Laboratory is prepared to provide for in-service training within localized hospitals upon special request regarding specific equipment and its application to either clinical or research applications. It is also in a position to provide for specialized training at the University of Maine in Orono upon special request.
6. Engineering — The presence of the physician/nurse/engineer team allows for solution of difficult problems of an interdisciplinary nature within hospitals and also for the solution of problems concerning multiple equipment interfaces.
7. Technological Consultation — The Laboratory is in a position to provide for telephone consultation concerning the applications of medical technology. Location within the university system allows access to specialized expertise outside the competence of the Clinical Engineering Laboratory Staff which is contained within the University. The Laboratory is also in a position to maintain cross reference files on facilities and services outside the university system and when appropriate it can make referrals to these agencies. In this fashion, the Laboratory acts as communication vehicle for exchange of information rather than actually performing services. The Laboratory Staff has had experience and is available by special contract to provide for extensive in-house consultation concerning management and development of complex hospital services. Areas of experience include design of intensive and critical care units, application of computer technology to clinical laboratory service and development and maintenance of telephone data transmission services.

At present, the Clinical Engineering Laboratory is a hospital oriented program based upon ultimate support by the hospitals of the State of Maine. The primary concern is making the medical technology within the hospital system function in the manner that it was designed. The Laboratory is not in a position to become involved with specific individuals or specific patients concerning unique individual medical problems.

The biomedical engineering expertise of the Clinical Engineering Laboratory could provide a resource for the development and support of both basic and clinical research programs in the State of Maine. It does not seem at all unreasonable to ex-

Continued on Page 118

Reserve these dates . . . June 5-8, 1976
123rd Annual Session
Maine Medical Association
Treadway-Samoset — Rockport, Maine

The Program for the Annual Session includes . . .

Monday, June 7

*Speakers and panel discussions presented by the Maine Medical Center,
Departments of Rheumatology and Orthopedics, Portland*

9:00 to 10:30 A.M.

"All You Need to Know About Rheumatism"

Moderator: ALBERT ARANSON, M.D.

10:50 to 12:00 Noon

"Orthopedic Contributions to Management of Aches, Pains and Deformities"

Moderator: LAWRENCE CRANE, M.D.

*Speakers and panel discussions presented by the Maine Medical Center,
Departments of Obstetrics-Gynecology and Pediatrics, Portland*

2:00 to 4:00 P.M.

"The High Risk Mother and Child"

Moderator: DOUGLASS W. WALKER, M.D.

Tuesday, June 8

Speakers presented by Tufts University School of Medicine, Boston

9:00 to 12:00 Noon

"Gastroenterology"

2:00 to 3:50 P.M.

"Pulmonary Disease"

EVENTS OF INTEREST —

Saturday, June 5

2:00 P.M. First Meeting of the House of Delegates

Presentation of the A. H. Robins' Physician Award for Community Service

Presentation of the Maine Blue Cross and Blue Shield "Award of Appreciation"

Sunday, June 6

A.M. Reference Committee Meetings

2:00 P.M. Second Meeting of the House of Delegates

Election of President-elect and Executive Committee District Members

SUNDAY EVENING — LOBSTER DINNER

MONDAY EVENING — ANNUAL BANQUET



Maine Blue Cross and Blue Shield News

80% UCR: DOES IT WORK?

Our Professional Relations representatives receive many questions from participating physicians regarding Blue Shield coverage. In this column we will attempt to answer those that deal with broad policy questions and that would seem to be of interest to most physicians' offices. We would welcome any suggestions for questions you would like to see addressed in this space.

To our surprise, the 80% UCR (80% Usual, Customary, & Reasonable) contract, introduced in 1974, received a mixed reception from participating physicians. Approved by the appropriate committees of the Maine Medical Association and Maine Osteopathic Association, the new contract generated controversy among physicians in the field almost from its inception. All county societies received a letter criticizing the new contract and a few of them adopted a resolution opposing 80% UCR.

The key issue was the service benefit income levels: \$6000 for an individual subscriber and \$9000 for a family. Following are the reasons for the development of the 80% UCR contract and the setting of the income levels:

1. By 1973, it had become clear that another level of coverage was necessary between BSD (which at that time was paying about 65% of physicians' charges) and full UCR (too expensive for many groups). One of the options considered was a higher fee schedule — a BSE contract.

2. Development of a BSE contract did not appear to be an attractive alternative. First, our single biggest complaint from both subscribers *and* physicians is that the BSC and BSD contracts leave the subscriber with an often unanticipated balance. The subscriber is unhappy with Blue Shield for paying less than he expected and perhaps unhappy with the physician for what he incorrectly assumes is overcharging. Secondly, the service benefit income levels for a BSE contract would logically have fallen in the \$6000 and \$9000 range. (The BSC contract, introduced in 1958, had income limits of \$4000 and \$6000. The BSD contract, introduced in 1967, had income limits of \$5000 and \$7500.) Moreover, the BSE contract would have fallen further and further behind actual charges, leaving subscribers with larger and larger balances and physicians with larger and larger amounts to write off for service benefit subscribers.

3. Therefore, we felt that an 80% UCR contract would be more in the interest of both subscribers *and* physicians. There should be predictability of payment and a constant percentage of unpaid balance. Moreover, we felt that the income limits would not impose a greater burden on the physician than heretofore. In 1974, 2.5% of BSC claims and 2.7% of BSD claims were service benefit. Given the fact that the higher contract would presumably be more marketable to more affluent groups, we anticipated that the percentage of service benefit claims under 80% UCR would be comparable to the percentages under the BSC and BSD contracts.

We were surprised, then, at the amount of controversy generated by 80% UCR. We were, and continue to be, convinced that the 80% UCR contract is better for both subscriber and physician than a fee schedule contract.

May we hear from you?

Necrologies

NORMAN E. COBB, M.D.

1902-1975

Dr. Norman E. Cobb, 73, of Belfast, Maine, died unexpectedly on September 19, 1975 at a Waterville hospital.

Born in Calais, Maine on July 18, 1902, he was the son of Walter and Mae Brown Cobb.

Dr. Cobb was graduated from Boston University in 1923 and received his medical degree from Boston University Medical School in 1927. He served his internship at the Massachusetts Memorial Hospital.

He practiced general medicine and surgery in Calais from 1928 to 1950; in Moreland, Oklahoma from 1950 to 1955; in Belfast from 1955 to 1975, retiring from active practice on September 13, 1975.

A senior member of the Waldo County Medical Society and the Maine Medical Association, he had served as Councilor for the Fourth District of the M.M.A. from 1968 to 1971. Dr. Cobb was also a member of the American Medical Association, the American Academy of Family Physicians and was a Fellow of the American College of Surgeons.

Surviving are his widow, Gladys Burns Cobb of Belfast; three daughters, Mrs. Maybelle Clark of Calais, Mrs. Barbara Madden of Omaha, Nebraska and Mrs. Betty Ann Vertullo of Hampton Beach, New Hampshire; one sister, Mrs. Edward Prescott of Brewer; six grandchildren and one niece.

DANIEL F. D. RUSSELL, M.D.

1879-1975

Dr. Daniel F. D. Russell, 96, of Leeds, Maine, died at his home on September 24, 1975.

He was born in Leeds on September 2, 1879, the son of Alonzo C. and Mary Richardson Russell.

Dr. Russell was graduated from Leavitt Institute and received his medical degree from Bowdoin Medical School in 1905. He interned at the Central Maine General Hospital in Lewiston and the Diagnostician Hospital in Boston.

He practiced in Leeds and surrounding communities until

shortly before his death. Dr. Russell was the town clerk of Leeds for twenty-five years and director of the Lewiston, Greene and Monmouth telephone company for many years.

An honorary member of the Androscoggin County Medical Association and the Maine Medical Association, Dr. Russell received a 70-year pin in June 1975. He was also a member of the American Medical Association.

Surviving is one niece, Mrs. Eula Carville of Leeds.

JOHN V. WARD, M.D.

1907-1975

Dr. John V. Ward, 67, of Falmouth Foreside, Maine, died on October 22, 1975 at a local hospital after a long illness.

Born in Portland, Maine on December 12, 1907, he was the son of Daniel E. and Susan Honan Ward.

Dr. Ward was graduated from Cheverus High School and Providence College and received his medical degree from Georgetown University Medical School in 1934. Following his internship and residency at St. Vincent's Hospital in New York, Dr. Ward located in Portland and practiced there and in Falmouth Foreside, retiring in 1970.

An affiliate member of the Cumberland County Medical Soci-

ety and the Maine Medical Association, he was also a member of the Board of the New England Obstetrical and Gynecological Society, the American Medical Association and a past president of the Mercy Hospital medical staff.

Surviving are a son, C. Daniel of New Canaan, Connecticut; a daughter, Mrs. Thomas C. Skolfield of Scarborough; two sisters, Mrs. George Bogner of Merrimac, Massachusetts and Mrs. Patrick F. Flynn of South Portland; two brothers, Willis L. of Bangor and Donald of Hollywood, Florida; two grandchildren, two aunts, an uncle and several nieces, nephews and cousins.

EUSTACHE N. GIGUERE, M.D.

1893-1975

Dr. Eustache N. Giguere, 82, of Lewiston, Maine, died on October 19, 1975 at the Marcotte Nursing Home after a long illness.

Born in Lewiston on September 19, 1893, he was the son of Philias and Dompille Marcous Giguere.

He was graduated from Bates College, received his medical degree from Bowdoin Medical School in 1921, and interned at the Maine Eye and Ear Infirmary in Portland.

Dr. Giguere was a member of the staff at St. Mary's General Hospital in Lewiston for over fifty years, serving as president of the staff in 1939. The hospital presented him an award in recognition of his dedicated professional service in 1972. He served as president of the Lewiston Parent-Teacher Association from 1936 to 1937 and was appointed a member of the Lewiston Charter Revision in 1938. A trustee of the Lewiston Public Library from

1940 to 1942, Dr. Giguere served as a member of the Lewiston Board of Education from 1942 to 1947 and as chairman from 1946 to 1947.

He was a member of the Student Army during World War I, and served in the Officer Reserve Corps of the Army. With the inauguration of the draft, he served as examining physician for the Androscoggin Local Board No. 1 of the Selective Service. During World War II, Dr. Giguere served as Androscoggin County Officer for the Procurement and Assignment Service for Physicians, Dentists and Veterinarians in the War Manpower Commission.

An honorary member of the Androscoggin County Medical Association and the Maine Medical Association, he received a 50-year pin in 1971. Dr. Giguere served as president of the Androscoggin County Medical Association in 1950, and was one

of the organizers of the Maine Chapter of the American Academy of General Practitioners of which he served as director.

Surviving are a daughter, Miss Madeleine Giguere; and two brothers, Lucien of Auburn and Origene of Lewiston.

HANS WEISZ, M.D.

1906-1975

Dr. Hans Weisz, 69, of Orono, Maine, died on November 18, 1975 at a Bangor hospital. An assistant director of medical services at Cutler Memorial Health Center at the University of Maine at Orono, he was stricken with a heart ailment while at work at the Center.

Born in Vienna, Austria on February 5, 1906, he was the son of Salomon and Rose Weisz.

A graduate of the Medical School of Vienna in 1929, with a doctorate in mathematics from the University of Vienna, Dr. Weisz was an assistant professor lecturing at the University of Vienna and engaged in private medical practice when Hitler's army marched into Austria in 1938. After a year of narrow escapes from arrest and help from doctors at Minnesota's Mayo Clinic who were familiar with his published work on electrotherapy, Dr. Weisz was able to make his way to London in 1939 and then to the United States in 1940.

His wife-to-be, Bertha Berner, escaped later from Austria, making her way to New York via Africa and Canada, and the couple were united at Ellis Island, married and made their way to Maine, where they have resided since.

Dr. Weisz worked for a summer at St. Mary's Hospital in Lewiston and was resident physician at the Rumford Community Hospital. Intrigued by rural practice, he found a town that needed a doctor — Howland — where he remained for five years before moving to the hospital in Lincoln. After 20 years at Lincoln, his desire to teach and work with young people took him to the University of Maine at Orono on August 1, 1966.

Dr. Weisz was a member of the Penobscot County Medical Society, the Maine Medical Association and the American Medical Association.

Surviving is his widow, the former Bertha Berner.

PERLEY J. MUNDIE, M.D.

1897-1975

Dr. Perley J. Mundie, 78, of Calais, Maine, died on November 27, 1975 at a local hospital.

He was born in Vanceboro, Maine on August 15, 1897, the son of Albert Robert and Eleanor Edith Mundie.

A graduate of Calais Academy and Bowdoin College, Dr. Mundie received his medical degree from Yale University School of Medicine in 1922. Following his internship at the Maine General Hospital in Portland, he did postgraduate work at

the University of Pennsylvania. In 1924, Dr. Mundie located in Calais specializing in otolaryngology.

An honorary member of the Washington County Medical Society and the Maine Medical Association, Dr. Mundie received a 50-year pin in 1972.

Surviving are a daughter, Mrs. Ronald O'Neill of Southington, Connecticut; and three grandchildren.

JOELLE C. HIEBERT, JR., M.D.

1924-1975

Dr. Joelle C. Hiebert, Jr., 51, of Norway, Maine, died on December 21, 1975 of a heart attack while en route to a Portland hospital.

He was born in Boston, Massachusetts on November 29, 1924, the son of Dr. Joelle C. and Susie P. Hiebert, Sr.

Dr. Hiebert was graduated from Lewiston High School in 1942 and was a championship debater. He also was graduated from Dartmouth College, where he was captain of the varsity ski team, and received his medical degree from Boston University School of Medicine in 1949. He interned at the Massachusetts Memorial Hospital and served a surgical residency there.

He served on the medical staff at the Central Maine General Hospital in Lewiston, moving to the Norway area in 1961 where he was affiliated with the Stephens Memorial Hospital. Dr.

Hiebert was also past president of the Northern Cumberland Memorial Hospital in Bridgton and at the time of his death was chief of surgery.

Dr. Hiebert was a member of the Oxford County Medical Society and the Maine Medical Association. An authority on Sandwich Glass, he had served as president of the National Early American Glass Club in Boston.

Surviving are a son, Mark W. of Kingfield; a daughter, Miss Diane R. of South Paris; his mother of Lewiston; two brothers, Dr. Clement A. Hiebert of Portland and Dr. Gordon L. Hiebert of Washington, D.C.; and two sisters, Mrs. Dorothy Odell of Alexandria, Virginia and Mrs. Ruth E. Davis of Osterville, Massachusetts.

ARTHUR H. MCQUILLAN, M.D.

1895-1976

Dr. Arthur H. McQuillan, 80, of Oakland, Maine, a prominent Waterville surgeon and one of the six physicians who founded Thayer Hospital in 1931 (now Mid-Maine Medical Center), died on February 24 at that hospital after a brief illness.

Born in Skowhegan, Maine on July 3, 1895, he was the son of Nathaniel and Esther Flanders McQuillan.

He was graduated from Skowhegan High School and Bowdoin College and received his medical degree from Harvard Medical

School in 1924. Dr. McQuillan interned at the Albany Hospital in New York and served a residency at the New York Lying-In Hospital.

In 1927, Dr. McQuillan started his practice in Waterville and was a member of the staff of both the Thayer and Sisters hospitals. He served as a member of the board of directors at Thayer Hospital from 1930 to 1947; as chief of surgery from 1937 to 1958; as vice-president of the board of trustees from 1938 to 1942; as

secretary of the medical staff for a number of years; and served on the honorary staff. He also served as a consultant in surgery for the Redington Hospital in Skowhegan and the Sisters Hospital.

An honorary member of the Kennebec County Medical As-

sociation and the Maine Medical Association, he received a 50-year pin in 1974. Dr. McQuillan was also a member of the American Medical Association and a Fellow of the American College of Surgeons.

County Society Notes

Kennebec

The Kennebec County Medical Association met at the Holiday Inn in Augusta, Maine on November 20, 1975, with a record turnout of 48 members and two guests. We were most honored to have in attendance, Dr. Euclid M. Hanbury, Jr., President of the Maine Medical Association. The President, Dr. Joseph J. Hiebel called the meeting to order at 7:30 p.m. The previous minutes were read and accepted.

Under old business, Dr. Martyn Vickers' application was voted on and he was accepted into membership. The application of Dr. Robert Roy was read. Under old business, the bylaws were referred back to the Bylaws Committee for further revisions before being submitted. Correspondence was read regarding the new prescription law and the Health Systems Agency Board. There was no new business to come before the meeting. The program was presented by Mr. William Carney, the Deputy Commissioner of the Bureau of Human Services, who talked to us about the Health Systems Agency, its current status, and some of its implications, about the Medicaid program, its costs and their method of surveillance of this program and briefly about the program. Dr. Hanbury briefly addressed the membership on the subject of the Maine Medical Association.

The meeting was enjoyed by the members and adjourned at 9:00 p.m.

The Kennebec County Medical Association met on December 18, 1975 at the Silent Woman in Waterville, Maine, with 23 members and guests present.

In the absence of the President, Dr. James C. Hayes called the meeting to order at 8:00 p.m. Minutes of the previous meeting were accepted as read.

Application of Dr. Robert I. Roy was read and voted on affirmatively.

A letter from Dr. Euclid M. Hanbury, Jr. to Commissioner Smith was read.

Election of officers was postponed due to the weather, which prevented members of the Nominating Committee from reporting.

Dr. Robert E. McAfee presented an informative discussion of the activities of the American Medical Association.

Meeting adjourned at 9:30 p.m.

O. THOMAS FEAGIN, M.D., *Secretary*

Lincoln-Sagadahoc

The regular monthly meeting of the Lincoln-Sagadahoc County Medical Society was held at The Ledges in Wiscasset, Maine on December 16, 1975.

Thirty-six members and guests attended. The meeting was called to order by the President, Dr. Ralph C. Powell at 8:55 p.m. The minutes of the November meeting were read and accepted as read.

The Board of Censors recommended that the Society elect Dr. Loren A. Olson of Brunswick to active membership; the nomination was unanimously accepted.

Dr. David W. Schall reported on last week's meeting of the House of Delegates of M.M.A. He stated that the Health Systems Agency Board of Directors includes three M.M.A. members out of sixty members; this was felt to be an undesirable representation. He stated that in January Medicaid will no longer cover dependent children until "reasonable attempts to collect from the absent parent" have been made by the physician. He

also noted that the House encouraged the State Department of Human Services to have physicians intimately involved in all E.P.S.D.T. programs.

Dr. Richard C. Leck amplified Dr. Schall's report and mentioned ways in which he hopes the present M.S.A. set-up will be overset. He reminded members that each must report his continuing education hours to M.M.A. and mentioned that in a few years, a prescribed minimum number of such hours may be necessary. He mentioned that AMA studies now in progress may recommend assessment of continuing competence of physicians by hospital staffs. He announced that the Executive Committee authorized the hiring of an Assistant to the Executive Director of the Maine Medical Association.

Dr. Robert H. Dixon read a letter from the Lincoln-Sagadahoc County Medical Society Auxiliary asking for interest in a joint meeting centered on psychosocial problems in physicians' families. The secretary was instructed to reply.

The nominating committee reported the following slate of nominees for office:

President: Dr. David S. Hill, Bath

Vice-President: Dr. Anthony J. Horstman, Boothbay Harbor

Secretary-Treasurer: Dr. George W. Bostwick, Newcastle

Delegates to the M.M.A. House of Delegates: Drs. David W. Schall, Brunswick and Horstman. Alternates: Drs. Gilbert R. Rowan, Bath and Frank O. Avantaggio, Jr., Damariscotta

Censors: Drs. Samuel L. Belknap, Damariscotta, John F. Dougherty, Bath and Carl R. Griffin, Jr., Boothbay Harbor

Program Committee: Drs. John F. Dumdey and Robert H. Dixon, both of Bath

Diabetes: Dr. Robert M. Hassan, Damariscotta

M.M.A. Health Care Financing Committee: Dr. Louis Bachrach, Brunswick

The motion was made, seconded, and voted unanimously that the secretary cast one ballot for the slate.

Dr. Dixon introduced Drs. Aldo F. Llorente and Richard Evans, III who spoke on the new commitment procedure for mental hospitals and showed the new commitment form. There was then a provocative exposition and discussion of the Total Woman.

GEORGE W. BOSTWICK, M.D., *Secretary*

Penobscot

The monthly meeting of the Penobscot County Medical Society was held at the Helm Restaurant on November 18, 1975 in Bangor, Maine. The meeting was opened by the President, Dr. Thornton W. Merriam, Jr. and several guests in attendance were introduced.

The minutes of the October meeting were read and approved.

Applications for membership in the County Society were received from the following individuals: Drs. Peter A. Rasmussen, Mark A. Feldman, John S. Kaiser and G. Douglas Timms. These applications were reviewed and approved by the Executive Council and subsequently unanimously approved by the membership.

It was noted for information that the new disclosure law provides the patient the right to know and have access to the contents of his medical record. This may have potential importance at all times, but it may be particularly important during disability evaluation determinations.

It was noted for information that the HP 176-LD200, an act relating to the prescribing and dispensing of drugs, goes into effect January 1, 1976. This law requires that all physician's prescriptions contain a square in the right hand lower corner of the prescription, accompanied by the appropriate paragraph which allows dispensing of generic medication unless the box is checked.

President Merriam presented a report of the Executive Committee of the Maine Medical Association. He noted that at the 1976 Annual Meeting of the Maine Medical Association, there will be no registration fee; however, courses will be held, and these will have a registration fee associated with them. He also noted the dues increased as previously announced, and finally, announced that an assistant to Dr. Dan Hanley is being actively sought for and that this assistant will be a non-physician.

It was announced that on November 25, 1975 a public meeting will be held in Bangor, Maine regarding the formation of the Health Systems Agency. Nominations for both providers and consumers for this agency were requested.

The Maine Medical Association informed the Penobscot County Medical Society that because of the increase in their membership that the County Society is permitted an additional delegate and alternate delegate to the House of Delegates of the Maine Medical Association. The name of Dr. John J. Pearson of Old Town for new delegate was presented and approved. Since Dr. Pearson had been an alternate delegate, two new alternate delegates were then presented and approved. These include Dr. A. Dewey Richards of Orono and Dr. William M. Blackwell of Millinocket.

A request from the Department of Health, Education and Welfare regarding approval of our County Society for their Hypertensive Screening Program was presented. After lengthy discussion, a motion was made to accept this proposal. The motion was seconded and defeated.

Following the business meeting, the speaker of the evening, Dr. Richard Chamberlin, was introduced. Dr. Chamberlin, as president of the Pine Tree Organization for Professional Standards Review, commented on the history of utilization review, the Medicare law, and PSRO. He traced the history of these acts from their legislative beginning and outlined where each stood at the present time. He likewise projected possible future developments in the area of PSRO, and its future implementation.

As there was no further business, the meeting was adjourned.

The monthly meeting of the Penobscot County Medical Society was held on December 16, 1975 at the Hilton Inn in Bangor, Maine.

The meeting was opened by the President, Dr. Thornton W. Merriam, Jr. and the minutes of the November meeting were approved as read.

President Merriam then introduced the several guests who were in attendance at the meeting.

Applications for membership into the County Society were then presented. Applications from the following individuals were heard. For active membership — Dr. John M. Long. For junior membership — Drs. Anne L. Hunter, Barbara B. Gibson, Michael B. Bruehl, Wayne D. Domin, Algis Vydas and C. Frazer Shipman. All applications had been previously reviewed and approved by the Executive Council. These applications were then voted upon by the full membership, and all were unanimously approved.

A communication from Dr. Donald M. Robertson regarding the status of the petition drive for the medical school of the University of Maine was then read. This letter commented upon the present status of the drive, as well as the plan for institution of further measures on behalf of the medical school in 1976.

A communication from Dr. John A. Woodcock, as Chairman of the Medical-Legal Liaison Committee of the Penobscot County Medical Society, was then read. This letter detailed the ongoing meetings which this committee is having with the Penobscot County Bar Association.

President Merriam read a copy of a letter from Dr. Euclid M. Hanbury, Jr., President of the Maine Medical Association, to Dr. Daniel Hanley, Executive Director of the Maine Medical Association, regarding his recent attendance at the Selection

Committee Meeting for the selection of the Board of Trustees for the Health Systems Agency. Following the reading of this letter, a lengthy discussion of this topic then followed. It was announced that the method of selection of the Board of Trustees for this agency would be protested by the Maine Medical Association. Dr. Thomas L. Watt made a motion, and it was seconded, that the Penobscot County Medical Society protest the selection of this Board of Trustees and that letters be sent to Governor Longley and Commissioner David Smith stating our objections. After discussion, Dr. Watt withdrew his motion. Dr. Paul H. LaMarche then made a motion, and it was seconded, that the Penobscot County Medical Society vote noncompliance with the Health Systems Agency Act. This motion was defeated. Dr. Watt then introduced a motion, and it was seconded, that the Penobscot County Medical Society forward a letter to Governor James Longley, Senator Edmund Muskie, Senator William Hathaway, Representative William Cohen, and Representative David Emery protesting the method of selection of the Board of Trustees of this Health Systems Agency and include in this communication our feeling that more doctors of medicine should be appointed to the Board in order to make this Board more representative of the methods of delivering health care. This motion was approved. Dr. A. Dewey Richards then moved, and it was seconded, that the Penobscot County Medical Society forward a letter to the three doctors of medicine who are members of the Board of Trustees of the Health Systems Agency, urging them to attend all future meetings of this Board and to voice strongly the feelings and concerns of the practicing physicians.

A report of the recent meeting of the House of Delegates was then read. Those in attendance at that meeting which was held on December 13, 1975 included Drs. Merriam, Kittredge, Richards, Leonidas, Phillips and Hunter. It was announced that Mr. Jeff Ackor would be offered the position of Assistant Executive Director of the Maine Medical Association. It was also noted that the Executive Committee of the Maine Medical Association voted to give \$10,000 to the Maine Burn Advisory Committee. In addition to the above, numerous other items discussed at that meeting were presented.

The Penobscot County Medical Society then voted to instruct their delegates to the House of Delegates to vote in favor of discontinuation of the Diabetes Detection Program in any vote taken for this program at the future House of Delegates Meeting.

It was announced that a public meeting of the Governor's Committee for Medical Malpractice would be held on December 17, 1975 in Bangor, Maine. Dr. Merriam will be appearing as a witness at that meeting and would be giving a formal presentation and answering questions given him by the committee.

Dr. Benjamin L. Shapiro made a motion, and it was seconded and passed, that the Penobscot County Medical Society forward a letter to the Commissioner of Human Services protesting the new regulation which states that reimbursement for medical care provided for children under the AFDC program be recovered from the responsible parent and that only in those cases where reasonable evidence at such attempt is presented will the State of Maine Department of Human Services provide that reimbursement.

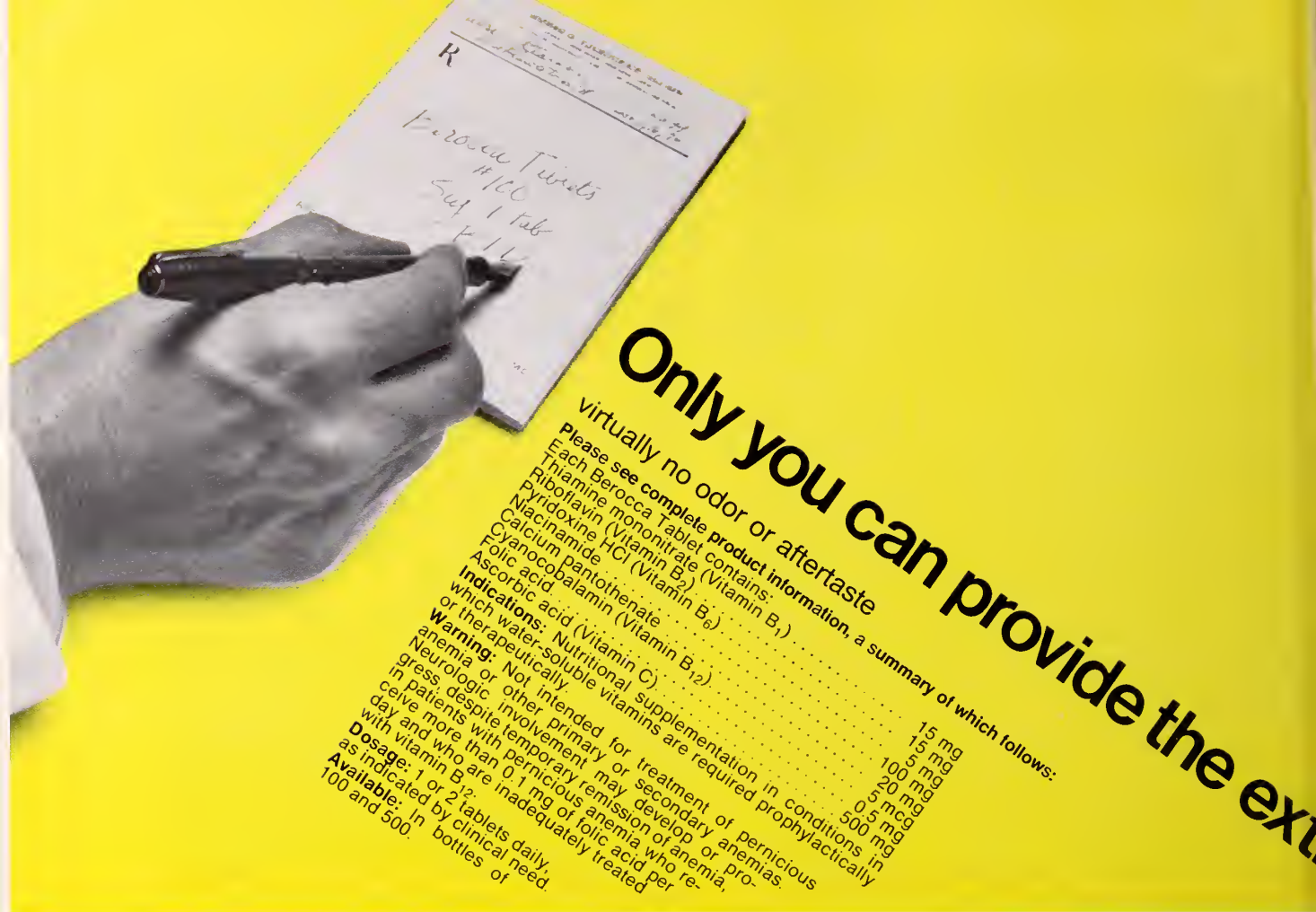
As there was no further business, the meeting was adjourned.

PHILIP G. HUNTER, M.D., *Secretary*

Androscoggin

The December 1975 meeting of the Androscoggin County Medical Society was held at Steckino's Restaurant in Lewiston, Maine on December 18, 1975 and was called to order at 8:10 p.m. by the President, Dr. Louis Fishman, with 47 members present. The Secretary read the minutes of the previous meeting which were then approved. Numerous pieces of communication were reviewed with the membership by the Secretary. Applications for membership as presented by the Credentials Committee for Drs. Michael C. Bach, internist and infectious diseases of Lewiston, Maine, and Gerald E. Davidson, psychiatrist, Elan 1, were presented and voted upon. Both doctors were welcomed into the membership for the County and State Medical Society.

Letter of resignation from Dr. Sawyer E. Medbury, Part-time



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Accident Room physician at St. Mary's Hospital, was read to the membership; and upon vote, the Executive Committee was empowered to look into the situation and determine whether remedy was possible, short of accepting Dr. Medbury's resignation.

The Secretary was directed to write a letter to Dr. Jan Knoppers; and by vote of the membership, his continuation in junior membership status did not appear to be justified on a continuing basis and that to maintain a full and active membership in the County and State Medical Society he would be required to submit full dues.

Resolutions in memoriam for Drs. Daniel F. D. Russell and Eustache N. Giguere were presented by Drs. Clapp and Carrier; and upon vote of the membership, these resolutions would be spread upon the books of the Androscoggin County Medical Society and be forwarded to the Maine Medical Association and copies directed to Dr. Russell's niece and Dr. Giguere's daughter.

The Executive Committee was directed to report at the January 1976 meeting in relationship to appropriate honorariums for both physicians.

The Secretary brought to the attention of the membership the requirements for increasing budgetary allowance for Assistant Secretary and office space. Upon direction, final report will be presented at the January 1976 Corporator's Meeting.

The Nominating Committee chaired by Dr. Gerard Morin presented the slate of officers for 1976. By unanimous vote, the following officers were elected:

President: Dr. Stanley D. Rosenblatt, Lewiston
 Vice-President: Dr. Charles A. Hannigan, Lewiston
 Secretary-Treasurer: Dr. Richard M. Swengel, Lewiston
 Councilor: Dr. Louis N. Fishman, Lewiston
 Delegate to the M.M.A. House of Delegates: Dr. Thomas F. Shields, Lewiston. Alternate: Dr. Mary T. Dycio, Lewiston

Following a short address by the outgoing President, Dr. Louis Fishman, the chair was assumed by Dr. Rosenblatt who voiced the appreciation to the Society for the many efforts of Dr. Fishman during his term as President of the Androscoggin County Medical Society. Membership was notified that the Annual Corporator's Meeting would be on January 15, 1976 at Steckino's Restaurant in Lewiston, Maine.

On duly seconded motion, the meeting was adjourned at 9:50 p.m.

The January 1976 Corporator's Meeting of the Androscoggin County Medical Society was held on January 15, 1976 at Steckino's Restaurant in Lewiston, Maine, with 39 members present. Minutes of the December meeting were read and approved as corrected. The Annual Treasurer's Report and Finance Committee Report were read and accepted with the provision of correction in the Finance Committee Report to be prepared by Dr. Otis Tibbetts. Dr. Charles W. Steele presented a short report from the Insurance Committee relative to the recent contract signed between the Maine Medical Association and the Veterans Administration for care of authorized veterans administration recipients.

Dr. Ross W. Green, chairman of the Legislative Action Committee, requested once again that his Committee be disbanded and its function to be assumed by the Delegates to the Maine Medical Association's House of Delegates. There was considerable discussion, and following a motion duly seconded to that effect, motion was defeated 11-6 with 22 abstentions. It is anticipated that the eleven gentlemen willing for retention of the Committee will be its most active supporters during this coming year.

Once again the status of Dr. Jan Knoppers was discussed at length, and the Secretary was directed to write him a personal letter to determine his official status on relationship to his train-

ing. The previous request from Dr. Sawyer E. Medbury relative to his resignation was reopened, and upon vote of the Society, the resignation will not be accepted and his name will be submitted to the Maine Medical Association House of Delegates to be placed in Affiliate membership status.

Following considerable discussion, it was moved, duly seconded, and voted by the membership to establish a permanent honorarium of \$100.00 in the name of our deceased members as is appropriate.

Membership application to the Androscoggin County Medical Society and the Maine Medical Association in the name of Dr. John Menges was accepted in transfer from the Lebanon County Medical Society, Lebanon, Pennsylvania. Upon report of the Credentials Committee, Dr. Menges was duly elected into the Society and welcomed into its membership.

Following discussion by the membership, it was moved and seconded to arrange certified audit of the books of this Society on an annual basis. Dr. Swengel, member of the Board of Trustees of the Maine Health Systems Agency, presented a short discussion of the organizational meetings and progress of the Health Systems Agency in Maine.

The meeting adjourned at 9:30 p.m.

RICHARD M. SWENGEL, M.D., *Secretary*

Waldo

A special meeting of the Waldo County Medical Society was convened at 4:15 p.m. by the President, Dr. T. Craig Childs.

Members present were Drs. Knuuti, Smith (Secretary-Treasurer), Hanbury, and Childs (President).

The Treasurer's Report showed a bank balance of \$388.48.

There was no old business.

New Business: Dr. Euclid M. Hanbury, Jr. proposed a quarterly meeting at Jed's Restaurant with speaker and dinner. The speaker's topic to be in the social or political sphere. It was further proposed that an annual assessment of \$40.00 be made to cover the cost of the dinner. The motion was seconded and unanimously passed.

The next meeting to be held March 31, 1976.

The following meeting to be held prior to the M. M. A. meeting in June.

The third meeting to be held in September.

The fourth meeting to be held in late November or early December.

There being no further business, the meeting was adjourned.

JOSEPH A. SMITH, M.D., *Secretary*

Cumberland

The December meeting of the Cumberland County Medical Society was held at the Red Coach Grill in Portland, Maine on December 18, 1975.

Applications for Membership - First Reading

Drs. Dermot N. Killian, Edward A. McCarthy and Carl J. Morrison.

Applications for Membership - Second Reading

Drs. J. Mark Kjeldgaard and James D. Miller.

New Business

It was voted that the Secretary of the County Medical Society (with the help of members of the Executive Committee) was to draft a letter expressing our dissatisfaction with Region I representation on the 60-member proposed board for the Health Systems Agency. Copies of this letter were to be sent to the Governor of the State of Maine, Commissioner of Health & Welfare for the State of Maine, and to the Region I office of the Health & Welfare in Boston, Massachusetts.

Announcements

Dr. Douglas R. Hill reported on the recent meeting of the Executive Committee of the Maine Medical Association.

Drs. Hill and Peter B. Webber reported on the matter of nursing home requirements relative to the recertification of patients and their respective patient care plans.

The matter of health systems agencies was discussed by Drs. Douglas R. Hill, John F. Gibbons and Douglass C. Pennoyer.

WESLEY J. ENGLISH, M.D., *Secretary*

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News, Notes and Announcements

Revised Meetings and Conferences — 1976 Maine Medical Center Portland, Maine

TIME	MEETING	PLACE	CHAIRMAN
WEDNESDAY			
Weekly			
8:00 A.M.	Continuing Education and Internal Medicine	NDF Classrooms #3-4	Dr. D. Wyman
12:00 Noon	Behavioral Science Seminar	MMC Family Practice Unit	Dr. R. True
FRIDAY			
Weekly			
12:00 Noon	Family Practice Grand Rounds	NDF Classroom #3	Dr. R. True

To Members of the Maine Medical Association:

RE: "THE CONDOR TRUST"

As a result of "The Condor Trust" situation in British Columbia and California, I feel it is well to again alert the members to the probability of other "schemes" which may be presented to various members of the Association. Apparently, the time is ripe for the promotion of schemes of varying credibility in view of the increasing difficulties that doctors and hospitals are having in procuring and maintaining professional liability insurance.

I ask once again to urge the members to be cautious in considering new schemes, and invite the members to utilize the services of the Maine Bureau of Insurance in determining the validity of any new organizations offering malpractice coverage.

FRANK M. HOGERTY, JR., Superintendent of Insurance, Department of Business Regulation, Bureau of Insurance, Capitol Shopping Center, Western Avenue, Augusta, Maine 04330

Two Humanities Seminars For Medical Practitioners To Be Supported In 1976 By The National Endowment For The Humanities

The National Endowment for the Humanities will again support a program of humanities seminars for physicians and other members of the health professions in 1976. The seminars will bring medical practitioners together with distinguished humanists from the fields of history, religion, sociology, and philosophy for a month of full-time study devoted to such issues as ethical conflicts, the rights of patients and practitioners, the purpose and limits of the medical professions and their relations to the community.

Up to 15 participants will attend each seminar tuition free and will receive a \$1,200 stipend to cover expenses, plus reimbursement for travel up to a \$300 maximum. Participants may be accompanied by members of their families, but the stipend will not be increased.

John C. Burnham, Professor of History and Lecturer in Psychiatry at The Ohio State University, will direct a seminar on his University's campus August 9-September 3. The aim of this seminar will be to identify the particular historical forces which have shaped the medical profession and determined the direction

of its development. It will attempt to sharpen the participants' understanding of their profession by studying it in the context of Western culture and how it has been involved in the forces of social change.

H. Tristram Engelhardt, Jr., a philosopher and physician who is Associate Professor of the Philosophy of Medicine in the Institute for the Medical Humanities of the University of Texas Medical Branch at Galveston, will direct a seminar at his University September 13-October 8. The seminar will examine the general issue of patient's rights and the particular issue of the right to health care through a consideration of the basic philosophical and ethical issues that bear on the status of the individual, the nature of justice, and the relationship between the individual and society.

Applications are invited from physicians and other members of the health professions, including public health officials, nurses, hospital administrators, executives of professional societies, and others. Selection of participants will be made by the seminar directors with the advice of selection committees. The application deadline for The Ohio State University and University of Texas seminars is May 13; selections will be announced about May 28.

Further information, including a leaflet describing the seminars in greater detail and application forms, may be obtained from: Professor John C. Burnham, Department of History, The Ohio State University, 230 West 17th Avenue, Columbus, Ohio 43210 and Professor H. Tristram Engelhardt, Jr., Institute for the Medical Humanities, University of Texas Medical Branch, Galveston, Texas 77550

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CLINICAL ENGINEERING, A POTENTIAL RESOURCE OF ENGINEERING SERVICES

Continued from Page 109

tend the sphere of influence of the Laboratory to include service to institutionally based research programs when such service is needed on a part-time or intermittent basis. The Laboratory could provide engineering services for clinical research programs

in small community hospitals where normally such support is not economically feasible. If there is interest in such research, the Clinical Engineering Laboratory would indeed be a potential resource.



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Coronary Bypass Surgery at the Maine Medical Center

A Progress Report

JEREMY R. MORTON, M.D., CLEMENT A. HIEBERT, M.D., CHRIS A. LUTES, M.D.
and RICHARD L. WHITE, M.D.

Between April 1972 and November 1975, 298 coronary bypass operations have been performed at the Maine Medical Center. The number of cases has increased rapidly from the outset (See Table 1) reflecting the prevalence of coronary disease and also the effectiveness of the coronary bypass procedure. The purpose of this communication is to report our experience to date with this procedure and to compare this experience with that of other institutions in the United States.

The patients ranged in age from 22 to 76 years with an average of 53. Half of the group had had at least one previous myocardial infarct and 65% had some degree of impaired left ventricular function judged on the basis of ventriculography. The majority of the patients had incapacitating angina pectoris unresponsive to medical management with nitrates and Propranolol and demonstrated a distinctly abnormal multi-level exercise test. One third of the patients had unstable angina requiring semi-emergent operation and occasionally pre-operative insertion of an intra-aortic counter-pulsation balloon.

Twenty-five patients underwent aortic or mitral valve replacement or resection of a ventricular aneurysm in association with one or more coronary bypass grafts. Of those with coronary grafts alone, 14 percent had single, 40 percent double, 32 percent triple and 14 percent had quadruple bypass grafts. In 12 patients, the internal mammary artery was employed as a pedicle bypass graft.

Postoperative complications were relatively rare, and most patients made a rapid and uneventful recovery. Approximately 30 percent developed

TABLE 1	
NUMBER OF CORONARY BYPASS CASES BY YEAR	
Year	Number of Cases
1972	3
1973	57
1974	127
1975 (To 10/1/75)	111
TOTAL	298

some type of arrhythmia usually ventricular ectopic beats requiring medication. Despite the very high incidence of cigarette smoking in the population, only six percent required respiratory support beyond the first postoperative day. Ten percent of the patients developed postoperative electrocardiographic evidence of myocardial infarction and an additional 20 percent showed elevation of cardiac enzymes suggesting some degree of intraoperative myocardial injury. Nonetheless, the clinical course of these patients was nearly identical to those without EKG or enzyme changes. The mean postoperative hospital stay was 12 days and only 20 percent remained in the hospital for more than two weeks.

MORTALITY

Of the 298 patients operated for uncomplicated coronary disease, four patients died for an early mortality of 1.3 percent. Two additional deaths occurred in patients operated for acute myocardial infarction with cardiogenic shock.

Four late deaths have occurred, three from cardiac causes, and one from stroke. One of these was at three months and the others beyond one

TABLE 2

NUMBER OF ASYMPTOMATIC PATIENTS FOLLOWING CORONARY BYPASS SURGERY	
3 Years	1
2 Years	20
1 Year	103
6 Months	47
Under 6 Months	67
TOTAL ASYMPTOMATIC	238 — 90%

year postoperatively. The overall cardiac mortality was therefore 3.0 percent. The mortality in patients operated for combined coronary and valvular disease or ventricular aneurysm was understandably significantly higher amounting to 20 percent in 1974 and 7.7 percent to date in 1975.

RESULTS

Current clinical follow-up information has been obtained on all patients operated prior to September 1, 1975 by examining the records of the local attending cardiologists or reviewing by telephone the records of the referring physicians. Two hundred thirty-eight or 90 percent of the 273 patients operated for isolated coronary disease have become asymptomatic and are leading normally active lives. Many patients, totally incapacitated with angina pectoris preoperatively, have returned to very vigorous activity without symptoms. Table 2 shows the length of follow-up for these patients. Twenty-five patients (10%) have experienced recurrent symptoms. While eleven of these, though still symptomatic, are significantly improved, the remaining 14 (4.7%) are no better than before operation.

FOLLOW-UP CATHETER STUDIES

Twenty-four patients have been restudied six months or longer after operation. Some of these were selected on a random basis while others were studied because of recurrent symptoms. Of the 49 grafts, 41 were open (See Table 3) for a graft patency rate of 84 percent. This figure is skewed somewhat since the patients were not all selected randomly, and the true graft patency rate for all patients would presumably be higher.

DISCUSSION

The operative mortality rate of 1.3 percent experienced in this series of patients as well as the clinical results compare favorably with the published figures of other institutions performing this surgery. These figures have been recently reviewed by Mundth and Austen¹ (See Table 4).

Operative mortality should also be compared with the mortality in patients having similar arteriographic lesions who have not undergone surgery. A group of 590 such patients who had coronary arteriography without surgery has been followed and reported by Bruschke, Proudfit, and Sones.¹⁸ The five year mortality in those with

TABLE 3

FOLLOW-UP CATHETER STUDIES (NOT RANDOM)		
24 Patients	49 Grafts	41 Patent 84%
	<i>Single Grafts</i>	6
	6 Patent	
	<i>Double Grafts</i>	13
	10 Both Patent	
	3 1 Patent	
	<i>Triple Grafts</i>	3
	1 3 Patent	
	1 2 Patent	
	1 1 Patent	
	<i>Quadruple Grafts</i>	2
	2 All Patent	

single vessel disease was 14.6 percent, those with two vessel disease was 37.8 percent, and those with three vessel disease was 53.8 percent.

Since 85 percent of the operated patients in the present series have two or more diseased vessels, the same group of patients treated without surgery would be expected to have a mortality of between five and ten percent per year. With surgery, on the other hand, the early mortality is 1.3 percent and the late mortality about 1 percent per year.

SUMMARY

Over 300 patients have undergone coronary artery bypass surgery in Maine with an operative mortality of 1.3 percent in patients with uncomplicated coronary disease. Postoperatively, 90 percent of patients are asymptomatic, 4 percent are improved, and 6 percent are unimproved. Twenty-five patients have had coronary bypass combined with valve replacement or ventricular aneurysmectomy with a significantly higher mortality. Postoperative complications have been few and relatively minor; the mean hospital stay has been 12 days. Mortality figures and clinical results in this series compare favorably with those of other institutions. Comparing these figures with an arteriographically similar group treated medically, the mortality is appreciably less in the surgically treated patients.

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TABLE 4

**CLINICAL RESULTS OF CORONARY ARTERY BYPASS
(AFTER MUNDTH & AUSTEN¹)**

<i>Institution</i>	<i>Source</i>	<i>Number of Cases</i>	<i>Operative Mortality %</i>	<i>Clinical Results Asymptomatic "Excellent" %</i>	<i>Late Mortality % Per Year</i>
Cleveland Clinic	Favaloro ²	1967	3.5		
Texas Heart Inst., Hous.	Cooley, et al ³	1492	7.1	62	2.4
Cleveland Clinic	Effler, et al ⁴	1323	3.2		
Texas Heart Inst. Hous.	Hall, et al ⁵	1276	6.6	62	2.3
Cleveland Clinic	Sheldon, et al ⁶	1000	4	85	2.5
Univ. Alabama	Kouchoukos, et al ⁷	548	3.5	52	
Baylor Univ., Hous.	Morris, et al ⁸	480	6.2		
St. Lukes, N.Y.C.	Hutchinson, et al ⁹	476	2.3	67	1.5
Univ. Wis., Milwaukee	Manley & Johnson ¹⁰	368	6	70	
Baylor Univ., Dallas	Adam, et al ¹¹	350	10	68	
St. Louis	Kaiser, et al ¹²	242	8.7		
Univ. Oregon	Anderson, et al ¹³	532	3.4	80	2.8
Peter Bent Brigham	Collins, et al ¹⁴	180	5.5	71	
Stanford Univ.	Alderman, et al ¹⁵	102	3.9	62	5.1
Mason Clinic, Seattle	Lawrence, et al ¹⁶	100	5.6	67	
Hahnemann, Phila.	Najmi, et al ¹⁷	100	12.0	72	
Maine Medical Center, Portland, Maine	Present Series	298	1.3	90	<1

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Reminder to M.M.A. Members

CONTINUING MEDICAL EDUCATION ACTIVITY REPORT

The bylaws of the Maine Medical Association were amended in June of 1973 as follows: Chapter I, Section 11, — "Each member of the Maine Medical Association shall be required to report his activities in continuing medical education every year according to a format provided by the Committee on Continuing Medical Education."

Only active, dues-paying members are required to report this year.

Please fill in your activity report promptly and return to the M.M.A. office, P.O. Box 250, Brunswick, Maine 04011.



Testing in Humans: Who, Where & When.

The weight of ethical opinion:

Few would disagree that the effectiveness and safety of any therapeutic agent or device must be determined through clinical research.

But now the *practice* of clinical research is under appraisal by Congress, the press and the general public. Who shall administer it? On whom are the products to be tested? Under what circumstances? And how shall results be evaluated and utilized?

The Pharmaceutical Manufacturers Association represents firms that are significantly engaged in the discovery and development of new medicines, medical devices and diagnostic products. Clinical research is essential to their efforts. Consequently, PMA formulated positions which it submitted on July 11, 1975, to the Subcommittee on Health of the Senate Labor and Public Welfare Committee, as its official policy recommendations. Here are the essentials of PMA's current thinking in this vital area.

1. PMA supports the mandate and mission of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research and offers to establish a special committee composed of experts of appropriate disciplines familiar with the industry's research methodology to volunteer its service to the Commission.

2. PMA supports the formation of an independent, expert, broadly based and representative panel to assess the current state of drug innovation and the impact upon it of existing laws, regulations and procedures.

3. When FDA proposes regulations, it should prepare and publish in the *Federal Register* a detailed statement assessing the impact of those regulations on drug and device innovation.

4. PMA proposes that an appropriately qualified medical organization be encouraged to undertake a comprehensive study of the optimum roles and responsibilities of the sponsor and physician when company-sponsored clinical research is performed by independent clinical investigators.

5. PMA recognizes that the physician-investigator has, and should have, the ultimate responsibility for deciding the substance and form of the informed consent to be obtained. However, PMA recommends that the sponsor of the experiment aid the investigator in discharging this important responsibility by providing (1) a document detailing the investigator's responsibilities under FDA regulations with regard to patient consent, and (2) a written description of the relevant facts about the investigational item to be studied, in comprehensible lay language.

6. In the case of children, the sponsor must require that informed consent be obtained from a legally appropriate representative of the participant. Voluntary consent of an older child, who may be capable of understanding, in addition to that of a parent, guardian or other legally responsible person, is advisable. Safety of the drug or device shall have been assessed in adult populations prior to use in children.

7. PMA endorses the general principle that, in the case of the mentally infirm, consent should be sought from both an understanding subject and from a parent or guardian, or in their absence, another legally responsible person.

8. Pharmaceutical manufacturers sponsoring investigations in prisons must take all reasonable care to assure that the facilities and personnel used in the conduct of the investigations are suitable for the protection of participants, and for the avoidance of coercion, with a respect for basic humanitarian principles.

9. Sponsors intending to conduct non-therapeutic clinical trials through the participation of employee volunteers should expand the membership and scope of its existing Medical Research Committee, or establish such an Internal Medical Research Committee, with responsibility to approve the consent forms of all volunteers, designs, protocols and the scope of the trial. The Committee should also bear responsibility to ensure full compliance with all procedures intended to protect employee volunteers' rights.

10. Where the sponsor obtains medical information or data on individuals, it shall be accorded the same confidential

status as provided in codes of ethics governing health care professionals.

11. PMA and its member firms accept responsibility to aid and encourage appropriate follow-up of human subjects who have received investigational products that cause latent toxicity in animals or, during their use in clinical investigation, are found to cause unexpected and serious adverse effects.

12. PMA supports the exploration and development by its member companies of more systematic surveillance procedures for newly marketed products.

13. When a pharmaceutical manufacturer concludes, on the basis of early clinical trials of a basic new agent, that a new drug application is likely to be submitted, a proposed development plan accompanied by a summary of existing data, would be submitted to the FDA. Following a review of this submission, the FDA, and its Advisory Committee where appropriate, would meet with the sponsor to discuss the development plan. No *formal* FDA approval should be required at this stage. Rather, the emphasis should be on identification of potential problems and questions for the sponsor's further study and resolution as the program develops.

The PMA believes that health professionals as well as the public at large should be made aware of these 13 points in its Policy on Clinical Research. For these recommendations envisage constructive, cooperative action by industry, research institutions, the health professions and government to encourage creative and workable responses to issues involved in the clinical investigation of new products.



Pharmaceutical Manufacturers Association

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Outpatient Arteriography*

PETER E. GIUSTRA, M.D. and PAUL J. KILLORAN, M.D.**

The Knox County General Hospital is a non-profit community hospital of eighty-nine beds. The limited number of available beds and the apparent absence of complications following arteriography made hospital admission for the purpose of overnight observation following arteriography seem unduly expensive and an unnecessary use of nursing personnel. Since 1971, it has been the policy of the Department of Radiology to perform arteriography on an outpatient basis whenever possible. The purpose of this paper is to report our protocol for outpatient arteriography and to discuss its merits.

PROCEDURE

Since January 1971, no patient has been admitted to the Knox County General Hospital solely for the purpose of arteriography. Arteriograms on an inpatient basis were those obtained in patients admitted to the hospital for acute medical or surgical problems. Excluding cardiac and neurovascular angiography, most types of arteriographic procedures have been performed. One hundred and fifty-two outpatients underwent 188 arteriograms, including 80 femoral, 45 aortoiliac, 25 renal, 9 celiac mesenteric, 21 aortic arch, 2 carotid, 3 brachial and 3 subclavian studies. More than one study via the same arterial puncture was performed on the same patient on fifteen occasions. There were 70 needle punctures without catheter introduction (64 femoral artery, 4 brachial and 2 carotid artery punctures) and 90 punctures with percutaneous catheter insertions (86 via the femoral artery and 4 via the axillary artery).

The arteriographic study is scheduled by the attending physician, usually directly through the radiologist, occasionally through the special procedure technician. Arteriography is performed in the late morning or early afternoon. The patient is instructed to omit the meal prior to the study. The arteriographic procedure is explained to the patient at the time of his arrival at the radiology department by the radiologist. Informed consent is verbal. No premedication is given. Ten milliliters of 1% lidocaine hydrochloride are used at the puncture site. Renografin®-60 (diatrizoate methylglucamine 60) is used for femoral and carotid arteriography. Renografin®-76 (diatrizoate methylglucamine 76) is employed for the other studies. Following termination of the procedure, the radiologist applies pressure over the puncture site until hemostasis is obtained. The patient is then placed on a

stretcher and observed in the radiology department for two to four hours. He is sent home to limited activity for the remainder of the day with instructions to apply pressure over the puncture site if swelling or bleeding should occur. The symptoms of arterial occlusion are explained. The patient resumes normal activity on the following day.

COMPLICATIONS

After being discharged from the radiology department, no patient has had to return to the hospital for complications from arteriography. Three patients were admitted to the hospital for complications immediately following the arteriography. These included an episode of transient hypotension in a 65-year-old man with progressive bilateral claudication following direct puncture left femoral arteriography. This patient had had five previous myocardial infarctions and was given 25 mg of Phenergan® intramuscularly before the study by his referring physician. The patient was admitted to the hospital in a normotensive state after spontaneous resolution of the hypotension and remained normotensive until discharged the following day. This was not considered a major complication. A 65-year-old woman with a chronic myeloproliferative disorder, massive splenomegaly and severe anemia underwent transfemoral abdominal aortography for a nonfunctioning left kidney. She bled at the puncture site ten minutes after apparent hemostasis. She was admitted for transfusion and overnight observation; signs and symptoms of septicemia developed, and the patient required parenteral antibiotic therapy. A 75-year-old man with a two-week history of progressive ischemic changes to the toes of the left foot underwent direct puncture femoral arteriography with two injections of 30 ml each of Renografin-60. Five minutes after the termination of the procedure with good hemostasis, tachycardia, pulmonary edema, ventricular fibrillation developed and the patient died despite resuscitative measures. Autopsy revealed a myocardial infarction approximately four weeks old with residual mural thrombus.

Since July 1970, when arteriography became routinely available at the Knox County General Hospital, 286 arteriograms have been obtained in 257 inpatients. Two major complications occurred, including catheter perforation of an abdominal aortic aneurysm and wire perforation of a narrowed atherosclerotic iliac artery. Both patients recovered under medical observation and treatment. No surgery was necessary. A large axillary hematoma developed in two other patients. These patients had received anticoagulation treatment with hep-

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arin, but we failed to receive this information before the axillary puncture. No treatment was necessary and both recovered without sequelae. These two hematomas were not considered major complications.¹ Thrombosis at the puncture site did not develop in any individual, either inpatient or outpatient. There were no cases of late hematoma or bleeding. Of a total of 474 inpatient-outpatient arteriograms, major complications, including one death, occurred in four patients. There have been no complications in either group since May 1974.

DISCUSSION

The complications from outpatient arteriography are no greater than those from inpatient arteriography. All the complications in 409 patients occurred during or immediately after the procedure. There were no known delayed complications. The State of Maine, although expansive geographically, is relatively close medically so that follow-up or word of complication is expected to be good. A single, small, regional hospital located in a rural setting is considered to be ideal for the performance of outpatient arteriography. Most patients are known by several of the physicians and hospital personnel. All patients are usually within reach if complications outside the hospital should occur. Traffic is not heavy, and roads are cleared effectively in the winter. All the small towns in the county have volunteer ambulance service.

Not only is the confined geographic area that we serve considered an advantage to the performance of outpatient arteriography, but so are the small size of the radiology department and the relatively small number of arteriographic procedures performed. Rarely are more than two arteriograms obtained in one day. This enables us to reasonably house the patient in the radiology department after the arteriography for a period of observation. Large institutions with a greater case load might have a problem in observing so many patients in the radiology department. Such observation would require added space, nursing personnel and stretchers. It would seem appropriate, however, to observe these patients in an outpatient surgery recovery area. Perhaps the building of observation areas in angiographic suites should be considered in the future. Our patients are observed by us every 15 minutes or so for two to four hours. None has stayed more than four hours, and most young patients are permitted to leave after two hours of complete hemostasis. In a 1963 national survey, thrombosis at the puncture site was the most common complication from arteriography.² Of ten serious complications in Moore's series of 1,204 cases, eight involved thrombosis at the puncture site, all occurring within four hours of the arteriography.³ Molnar¹ reported that thrombosis of the axillary artery occurred in nine patients immediately following arteriography.

Verbal informed consent is felt to be the least anxiety producing⁴ and is obtained from the patient in the radiology department at the time of arteriography. Because it is important to us that the patient be kept alert during the procedure to communicate any discomfort or questions and to permit evaluation of changes in sensorium, no premedication is given. No patient has refused multiple injections where deemed necessary, and only one patient requested general anesthesia when a repeat arteriogram at a later date became necessary.

Pressure over the puncture site is held by the radiologist usually for ten minutes until hemostasis is obtained. Sometimes hemostasis is obtained after five minutes, sometimes not until twenty minutes. This period of manual pressure is considered very important in preventing hematoma or subsequent bleeding. Only one patient of 409 bled after apparent hemostasis. She had an underlying coagulopathy secondary to a chronic myeloproliferative disorder. In a large institution, it may not be the practice for the radiologist to maintain pressure. Perhaps more hematomas and bleeding might occur which would make admission to the hospital more common than has been the case in our institution. We have no experience with the mechanical pressure devices. Their apparent efficiency might be a distinct advantage to the larger angiographic department.

Who pays for these outpatient procedures? In the State of Maine, the major contract third-party payers cover outpatient radiology services. In other states where insurance might not cover outpatient radiology, it becomes a matter of economics to admit patients for angiography to spare the patient out-of-pocket expenses. Even in those instances where individual insurance does not provide for outpatient radiology, collection from our outpatients has been excellent.

A drawback to this study might be the relatively small number of patients examined compared to those reported from larger institutions. This study, however, covers a four and one-half year period and, for a hospital staff of our size, represents an active arteriography program. With more residents being fully trained in special procedures under the three-year diagnostic radiology program and subsequent fellowships, more smaller institutions are finding themselves with radiologists capable of performing angiography. We presume the same is true nationally, and therefore our experience may be applicable to many more institutions than would have been the case ten years ago. It may be that some increased risk is to be expected in a small department per se. We feel, however, that our complications occurred in high risk patients. Either the patients had severe atherosclerotic disease or underlying pathology, as in the case of a patient with recent myocardial infarction and one with myeloproliferative disease. Complications in such

Continued on Page 127

Obturator Hernia

A Case Report

ERIC E. GORANSON, M.D. and PADIATH A. ASLAM, M.D.

Herniation of abdominal contents into the obturator canal is rare. Since the first two cases were presented in 1724, there have been only 492 cases reported in the medical literature. This paper describes a case of obturator hernia with an unusual presentation.

CASE SUMMARY

A 65-year-old white female was admitted to Augusta General Hospital for intestinal obstruction. She was having colicky abdominal pain, nausea and vomiting which had begun four days prior to admission. There was no recent weight loss. She had had only one soft bowel movement in the four days prior to admission.

When first seen, she appeared acutely ill and thin, with marked distention of the lower abdomen. During the examination, she vomited several times, bringing up guaiac-positive material. Auscultation of the abdomen revealed high-pitched bowel sounds. She was moderately dehydrated and afebrile. Bibasilar rales were heard which cleared with cough. No mass was felt on rectal or pelvic examination, and she did not complain of any pains in her thighs or knees.

WBC was 13,200 with 68% polys and 5% bands. Chest X-ray showed a left lower lobe infiltrate. Abdominal X-ray series showed partial small bowel obstruction.

On the assumption that she had a paralytic ileus secondary to pneumonia, she was given antibiotics and placed on nasogastric suction. The infiltrate rapidly cleared, but the distention, after slight initial improvement, remained. Abdominal series continued to show partial small bowel obstruction. On the 7th hospital day, she underwent exploratory laparotomy. A knuckle of distal jejunum was trapped in the obturator canal and was nonviable and perforated. The hernial defect was repaired and an end-to-end anastomosis was done. She improved gradually and was discharged from the hospital on the 24th day.

COMMENT

In 1724, the first two cases of obturator hernia were presented to the Royal Academy of Science in Paris by Pierre Rolane Arnaud de Ronsil. Two years later, Camper first described the anatomy of this type of hernia. In 1768, G. de Ronsil, son of Arnaud, described the first case of obturator hernia successfully reduced by taxis. The first laparotomy for this condition was performed in 1848 by Hilton.¹

This hernia is six times more common in females than in males. The reasons for this preponderance are: 1) a normally larger and wider obturator canal in females, 2) relaxation of the pelvic peritoneum due to repeated pregnancies,^{2,3} and 3) a more vertical obturator canal in males.⁴ Although Watson⁵ reported a case of obturator hernia in a 12-year-old patient, most patients are over 50,⁶ the average being in the 7th and 8th decades.³ Males appear to be affected earlier in life than females.⁴ There is usually a history of recent weight loss, the contributing factor being loss of extraperitoneal fat. In emaciated patients, the hernia occurs about equally

on either side. In non-emaciated patients, the hernia occurs on the right side nearly four times more often than on the left. The right-to-left incidence is about equal in the male and about 3-to-1 in the female.

The hernias are usually small and possess a peritoneal sac. Usually, they contain only small intestine, but they may also contain omentum, sigmoid epiploicae, bladder, Meckel's diverticulum, fallopian tubes or cecum with appendix.^{3,4} Partial strangulation (Richter's hernia) occurs commonly in obturator hernia,⁶ as it did in our patient.

Because of its rare occurrence, the diagnosis of obturator hernia is usually made at laparotomy. Recent surveys of the literature have shown that preoperative diagnosis of obturator hernia was made in from 24 to 30% of cases,^{1,4} and it has been suggested⁴ that the preoperative diagnosis of this condition may be no better today than it was a century ago.

Signs and symptoms of intestinal obstruction are frequently found in patients with obturator hernia. The obstruction may be partial, as in our patient, or complete. It may be recurrent and intermittent, or acute and progressive. There is abdominal pain, vomiting and distention in nearly all cases.

In more than half the patients, the Howship-Romberg sign is present. This sign consists of pain or paresthesias along the medial surface of the thigh down to the knee, the area supplied by the obturator nerve, and is produced by pressure on the obturator nerve as it passes through the obturator canal. It is made worse by extension, abduction or internal rotation of the thigh, and the patient commonly attempts to relieve the pain by flexing, externally rotating or adducting the thigh. This sign is considered by some to be pathognomonic of obturator hernia, but, although Shackelford⁶ states that obturator neuralgia is uncommon except when caused by obturator hernia, it may also be produced by tumors of the pelvic organs or by the stress on pelvic structures occurring during vaginal hysterectomy. Our patient did not exhibit the Howship-Romberg sign.

There may be a palpable mass on rectal or vaginal examination. The best way of palpating the obturator canal is with the thigh flexed, adducted and externally rotated. If the hernia is complete, there may also be a fullness in the obturator area of the thigh. Tenderness or pain over the mass may mean that strangulation is present.

Obturator hernias should be repaired surgically. The earlier the surgery is done, the better the prognosis for the patient, as delay increases the probab-

ity of strangulation, necrosis and perforation. In Watson's collected series for the period 1890-1948,⁵ the overall mortality rate was between 60 and 85%. On those patients treated surgically, mortality was 30%. Recent reports show still lower rates.^{1,2,3,4}

There are several methods of approach in the surgical repair of obturator hernia. These are described in detail by Shackelford. The abdominal approach is best because it is easy, safe, and it permits diagnosis and resection, if needed.

Shackelford reported a recurrence rate after operation of 10%.⁶ He did not say what the recurrence rate is of patients in whom the hernial defect has been repaired. Gray⁴ reported fifty cases, all but thirteen of which had repair of the defect and in which there was only one recurrence. He did not say whether that case had had repair of the defect. Ang¹ reported four cases in which no repair was done, and in which there has been no recurrence. He stated that repair may be contraindicated or unnecessary in cases where infection and inflammation around the sac occurred, secondary to gangrene and perforation. He reasoned that post-inflammatory fibrosis may be sufficient to repair the defect.

SUMMARY

Our patient presented with colicky abdominal pain, distention and a pulmonary infiltrate, but had neither a palpable pelvic mass nor the Howship-Romberg sign. Because it was not thought of and because of the pulmonary infiltrate, the diagnosis was missed preoperatively. Although obturator hernia is rare, this should serve as a reminder for the physician to think of obturator hernia, especially in thin, elderly patients who present with signs of intestinal obstruction.

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OUTPATIENT ARTERIOGRAPHY — Continued from Page 125

patients might occur in any department, regardless of size. In the patient with myeloproliferative disease, the indication for arteriography was questionable and, in retrospect, this patient probably should not have had arterial puncture with catheter insertion.

The average age of our outpatients was 58 years, the oldest being 95 and the youngest 5 years old. Forty percent of the outpatients were over the age of 65 years. This partially reflects the more aged population in our area when compared to other parts of the country, but in general arteriography is performed more commonly in older individuals.² Our three outpatient complications occurred in patients aged 65 years or older.

A certain number (not recorded) of small hematomas at femoral puncture sites have occurred over the years, but there were no massive femoral hematomas. The number of catheter changes and repeated injections were not consistently recorded

but seem no greater in the inpatient versus the outpatient group. We wish to stress that all the complications occurred during or immediately after the arteriography. There were no instances of delayed bleeding, hematoma or thrombosis at the puncture site. We know of no false aneurysm formation, although such aneurysms can be small and may go unrecognized by the patient for some time. Thrombophlebitis did not develop in any patient.

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Department of Health and Welfare

Sudden Infant Death Syndrome in Maine

HELEN M. ZIDOWECKI*

In October 1973 the Sudden Infant Death Act, which was passed by the 106th Legislature, went into effect as part of the Department of Human Services Laws, Title 22, Section 3026. This Section requires a Medical Examiner to submit a report within 72 hours to the Chief Medical Examiner for each child under 3 years of age who dies unattended by a physician. This report may be sent by the Chief Medical Examiner to the Bureau of Health, namely the Director of the Division of Public Health Nursing. The Division of Public Health Nursing staff, or staff from a local nursing agency, contacts the family 1) to provide information regarding SIDS; 2) to provide emotional support to the family and possible referral for further support; and 3) to obtain some information regarding the condition of the child prior to death. The description of this program appeared in *The Journal of the Maine Medical Association*, Volume 65, No. 4, p. 93 to 95, April 1974.

In the two years in which the program has been in effect, namely calendar years 1974 and 1975, there has been an increased awareness of SIDS. In 1974, 30 SIDS came to the attention of the Division of Public Health Nursing; in 1975, 42 SIDS. The increase between 1974 and 1975 probably can be attributed to increased awareness of the syndrome and the program, rather than to an increase in incidence. Specific characteristics of children reported for 1975 are given in Table 1.

TABLE 1

SELECTED CHARACTERISTICS OF 42 SIDS REPORTED TO DIVISION OF PUBLIC HEALTH NURSING, 1975		
Characteristic	Number	% of Total (42)
Age at death — 1 month	6	14
2 months	15	36
3 months	8	19
4 months	3	7
5-12 months	8	19
12-20 months	2	5
Sex — Male	19	45
Female	23	55
Premature birth	2	5

*Director, Division of Public Health Nursing

TABLE 2

PROGRAM FACTORS IN 42 SIDS CASES, 1975		
Program Factors	Number	% of Total (42)
Location of Child at Time of Death, Department of Human Services Regions.*		
Region I—Cumberland County	8	19
York County	3	7
Region II—Androscoggin County	8	19
Franklin County	2	5
Oxford County	6	14
Region III—Kennebec County	2	5
Somerset County	3	7
Knox County	1	2
Lincoln County	1	2
Sagadahoc County	0	0
Waldo County	0	0
Region IV—Penobscot County	3	7
Piscataquis County	2	5
Hancock County	1	2
Washington County	2	5
Region V—Aroostook County	0	0
Urban — Portland	4	10
Lewiston, Auburn	5	12
Bangor	3	7
Medical Examiner's Report or Autopsy Rec'd.		
Within 72 hours	8	19
4-7 days	16	38
8 days-1 month	14	33
1+ month	2	5
Not received as of 1/9/76	2**	5
Nursing Visits —		
Family contacted, nursing report completed	30	71
Family moved or unable to locate	5	12
Nursing reports not received as of 1/9/76	7**	17

*2 children resided out of state and were visiting relatives in Maine at time of death.

**Includes SIDS which occurred in December 1975.

The focus of the program has been on service provided to the immediate and extended family. Information regarding the child's condition prior to death, and a history of other SIDS in the family, has been obtained informally. Many children have had respiratory problems, such as colds, frequently accompanied by fever and diarrhea. Some have

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Tardive Dyskinesia

KURT E. CLYNE, B.S. and RANDY P. JUHL, Ph.D.

ABSTRACT

Tardive dyskinesia is an often disabling disorder which in its classic form consists of involuntary movements of the lips, jaws and tongue. Present attempts to treat this antipsychotic drug-induced syndrome include the use of dopamine depleting or blocking drugs and cholinergic stimulating drugs. Because no specific treatment has been uniformly successful in alleviating the symptoms of tardive dyskinesia, preventive measures, including the rational use of antipsychotic agents, should be incorporated into each practitioner's prescribing practices.

INTRODUCTION

Tardive dyskinesia (TD), also called "terminal extrapyramidal insufficiency," "complex dyskinesia," and "persistent dyskinesia," is a clinical entity observed with increasing frequency since it was first reported in the late 1950's.¹⁻⁸ The syndrome was initially called "perioral dyskinesia" because the lower mouth was frequently involved. As it became apparent that muscle groups throughout the body were affected, the term "tardive dyskinesia" became popular.⁹

This neurologic disorder can occur as a result of several weeks or months of antipsychotic drug administration but usually occurs after several years of treatment.¹⁰ The onset of symptoms may occur during or following treatment with antipsychotic drugs. Females tend to be afflicted more frequently than males (3:1),^{2,11,12} and an increased susceptibility to TD seems to occur past the age of 50 years.^{2,13} However, TD has also been observed in children.¹⁴⁻¹⁶ In addition, it is reported that brain damage may predispose a person to TD^{11,17} but is not a necessary factor.¹⁸ Attempts to treat TD with various drugs have yielded conflicting results.

From 1958 to 1971, 1,800 cases of TD were reported in the literature; 1,200 of these occurred between 1968 and 1971. The incidence of this disorder in patients treated with antipsychotic drugs is re-

ported to be as low as 0.5% to as high as 40%.¹⁹ Clearly, the frequency of the events depends upon how well it is recognized and how closely it is looked for. Increasing recognition and understanding of the syndrome may partly explain the higher incidences quoted recently. Furthermore, the presence of TD *per se* may be a criterion for keeping patients hospitalized, thereby biasing incidence figures in the upward direction. Nevertheless, in light of the estimated 250 million patients who received antipsychotic drugs prior to 1971,²⁰ it is evident that TD is a potentially common disability.

CLINICAL DESCRIPTION

The classic symptom of TD is a "buccolinguo-masticatory" triad which consists of involuntary movements of the lips, jaws and tongue. Characteristic manifestations include sucking and smacking movements of the lips, lateral jaw movements, puffing of the cheeks and thrusting, rolling and fly-catching movements of the tongue.¹⁰ These abnormal movements of the lips and tongue are often socially objectionable and thus are a source of considerable embarrassment to the patient and his family. Speech may become dysarthric to the point of being incomprehensible,²¹ and difficulty in swallowing may result in a considerable loss of weight.²² These symptoms often worsen under emotional tension and disappear during sleep.¹⁰ Furthermore, TD and parkinsonism may coexist and make diagnosis of either difficult.²³

In addition to facio-oral dysfunctions, the patient may develop either slow, worm-like athetoid or quick involuntary choreiform movements of the limbs. Circular movements of the big toe have been noted by some clinicians to occur frequently. Severe dystonia involving muscles controlling the balance of the body may be painful and thus greatly reduce the patient's activity. These symptoms may progressively worsen and are considered to be irreversible in a high percentage of cases.¹¹ It is thought that one of the earliest signs of developing TD is a slow, worm-like (vermicular) movement of the tongue.² Consequently, periodic examination of the tongue provides a convenient, early detection technique.

ETIOLOGY

There is little doubt that the prolonged administration of antipsychotic drugs plays a major role in the development of TD.^{11,24,25} Besides phenothia-

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zines, the thioxanthenes, butyrophenones, dibenzoxazepines and dihydroindolines also possess the potential for inducing TD.^{1,10,26} The question of whether a particular class of neuroleptics is more likely to produce TD is largely unanswered. Investigation of this question has produced inconclusive and contradictory results.^{2,12}

Even though TD is usually thought to develop after prolonged treatment with antipsychotic drugs, many patients, particularly the elderly, develop TD after receiving moderate doses of these drugs.¹¹ Evans reported a patient who developed an oral dyskinesia following only four months of treatment with 3-4 mg/day of trifluoperazine.²⁷ Jacobsen reported four cases of dyskinesia attributable to haloperidol treatment (4-20 mg/day) for less than two years.²⁸ Additionally, daily doses of chlorpromazine (75 mg) administered for three months have been reported to cause oral dyskinesias.¹¹

Recently, Crane attempted to quantitate the total intake of antipsychotic drugs in relation to TD symptomatology.¹² Of the patients with intakes greater than 16.2 gm chlorpromazine equivalent, 53% manifested TD of at least moderate proportions, while only 10% of those receiving less than 16.2 gm were so affected. Crane concluded that moderate and moderately severe dyskinesias were detected only in persons who had received a minimum daily dose of 75 mg chlorpromazine equivalent. Unfortunately, because the dosage requirements for most schizophrenic patients exceed these limits, Crane's criteria excludes very few patients from risk of developing TD.

TD may arise unnecessarily as the result of improper selection of patients for antipsychotic drug treatment. This may be illustrated by two examples. First, TD has developed in nonpsychotic children who have received antipsychotic agents.¹⁴ The existence of this syndrome in children is disastrous. Secondly, TD has occurred in adults following the use of antipsychotic drugs for anxiety neurosis and other nonpsychotic disorders.²⁹ Therefore, the decision to use antipsychotic drugs in unsocialized, aggressive or hyperkinetic children and patients with severe anxiety must be weighed carefully.

Also of much concern are reports of a TD-like syndrome following the administration of drugs other than antipsychotic agents. These include methylphenidate,^{30,31} dextroamphetamine,³² and antihistamines.^{33,34}

PHARMACOLOGY OF TARDIVE DYSKINESIA

At the present time, the pathogenesis and pathophysiology of TD remains a matter of conjecture. It is probable that a variety of pathophysiological mechanisms are involved.^{18,35} It is commonly thought that TD is related to excessive dopaminergic activity in the brain which results from prolonged antipsychotic drug administration.¹⁰

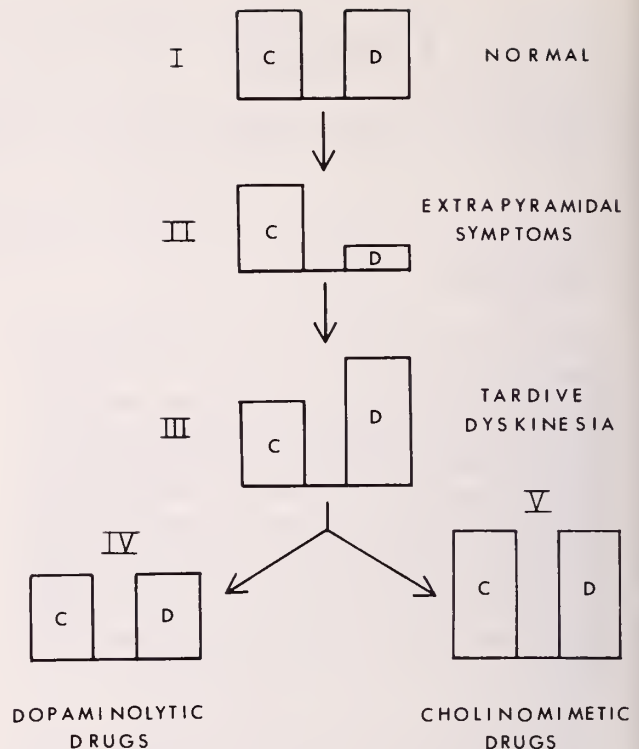


Fig. 1. A schematic representation of the equilibrium between the cholinergic (C) and dopaminergic (D) systems in the brain under various conditions. I. Normal equilibrium: no drug therapy. II. Suppressed dopaminergic tone due to antipsychotic treatment resulting in extrapyramidal symptoms. III. Excess dopaminergic tone caused by antipsychotic-induced denervation of the dopamine receptors resulting in TD. IV. Restoration of cholinergic-dopaminergic equilibrium by the administration of dopamine depleting or blocking drugs. V. Restoration of cholinergic-dopaminergic equilibrium by the administration of cholinergic stimulating drugs.

In the normal individual, there exists a mutually antagonistic effect between the cholinergic and dopaminergic systems upon the striatal cells in the brain. A balance between the two systems, as schematically represented in Figure 1-I, is necessary for normal motor functioning.^{18,36}

The antipsychotic agents are thought to block the dopamine receptor sites located in the neostriatum (caudate nucleus and putamen), and in the substantia nigra. Since schizophrenia might be caused by disturbances of dopamine function, the antipsychotic effect of these drugs might be related to this blockade.²⁶ Dopaminergic blockade results in a relative cholinergic dominance in the striatal portion of the brain (Figure 1-II). This imbalance is thought to be the origin of the extrapyramidal symptoms such as dystonia, akathisia, or Parkinson's disease, which are frequent side effects of antipsychotic drugs.^{4,37} These neurologic symptoms may be treated by elimination of the dopamine blockade through dose reduction, or by the use of an anticholinergic drug to reestablish a relative balance between the cholinergic and dopaminergic systems.

It is postulated that the treatment of schizophrenia by prolonged dopaminergic blockade eventually induces a "chemical denervation" of the dopaminergic receptors.^{38,39} These receptors are thus rendered super-sensitive to dopamine. Therefore, if dopamine blockade is diminished by discontinuation of the antipsychotic agent or by a dosage reduction, the system responds in an exaggerated manner to what would otherwise be a normal level of dopamine input. It is this relative excess of dopaminergic tone that is thought to underlie the clinical manifestations of TD (Figure 1-III).

The effects of levodopa, reserpine, cholinergic and anticholinergic drugs have strengthened the dopamine theory of TD. Parkinsonian patients treated with levodopa frequently develop a dyskinesic syndrome resembling TD.³⁹ It is possible to suppress this drug-induced dyskinesia with antipsychotic agents through dopamine blockade. Also, patients with TD experience an exacerbation of their disorder when given levodopa.^{40,41} Reserpine, on the other hand, which depletes dopamine stores of the brain, diminishes the symptoms of TD.¹⁰ In addition, cholinergic stimulants, such as physostigmine, have been reported to suppress dyskinesic movements,³⁶ while anticholinergics exacerbate the symptoms.⁴²⁻⁴⁴ These observations are consistent with the dopamine theory and suggest that levodopa and anticholinergic agents should be avoided in patients with TD.

Besides the effects on synaptic transmission, the antipsychotic drugs may also have a toxic effect on nervous tissue.⁴⁵ By interference with membrane function and inhibition of the respiratory enzymes in nerve cells, phenothiazines may produce organic brain lesions. These lesions have been suggested as a possible cause of dyskinesia.²⁶ Post-mortem investigation of 28 human brains obtained from patients with oral dyskinesias by Christensen revealed that lesions of the substantia nigra, midbrain and brain stem were more common in these patients than in a group of controls matched for age and sex.⁴⁶ Nashold localized the pathology underlying the oral-facial-lingual syndrome in the central tegmental region by stereotaxic procedures.⁴⁷ He concluded that the functioning area seems to lie in the upper brain stem. Gross anatomical lesions in the brain or its vascular system have been ruled out as a possible cause of TD.²

The dopamine theory offers a convenient, even if simplistic, explanation of the etiology of TD. However, further long-term investigation is necessary to provide a satisfactory and comprehensive explanation for the many puzzling features of this antipsychotic-induced neurological disorder.

TREATMENT

If the dopamine theory is a primary etiologic factor in the development of TD, then the reestablishment of a relative balance between the dopaminergic and cholinergic systems would be ex-

pected to suppress dyskinesic symptoms. Attempts to restore this equilibrium have followed two basic approaches. First, the administration of drugs which block access of dopamine to the receptor sites or deplete the interneuronal stores of dopamine would increase dopaminergic tone and thus reestablish balance (Figure 1-IV). Conversely, equilibrium may be attained by increasing the level of cholinergic activity in the brain with a cholinomimetic (Figure 1-V).

Dopamine Depleting Agents

Reserpine. This dopamine depleting agent has been used to treat TD with variable results.^{48,49} Villeneuve reported that 43% of the patients in one group receiving reserpine (0.75-1.0 mg/day) without regular phenothiazine medication showed improvement following four weeks of treatment. This is compared to a second group of patients which demonstrated only 19% improvement while receiving reserpine plus a phenothiazine.⁴⁸ It has been demonstrated in animals that chlorpromazine inhibits reserpine's ability to lower brain serotonin, norepinephrine and dopamine levels.⁵⁰ Therefore, this may have been the cause of less impressive results in Villeneuve's second group of patients who received concomitant phenothiazine medication.

With doses of reserpine greater than 1 mg per day, side effects such as agitation, paranoid ideation and orthostatic hypotension often necessitate a decrease in dosage. Although doses of up to 5 mg per day have been utilized, it was felt that 1 mg offered optimal control while minimizing side effects.⁴⁹

In view of potential phenothiazine inhibition of reserpine, a problem arises in the management of patients with dyskinesia, since reserpine alone is a weak antipsychotic drug.⁵⁰ Despite the drug's effectiveness, the slow onset of reserpine (one to two weeks) is a disadvantage to the patient requiring prompt relief of painful dyskinesia.

Tetrabenazine. This experimental drug has also been used to treat TD. Compared with reserpine, it acts more rapidly and possesses less hypotensive activity. Three short-term studies of the effectiveness of tetrabenazine revealed encouraging results.⁵¹⁻⁵³ Of the 32 patients in these studies, 21 showed marked improvement following six weeks of treatment.

In an attempt to explore the long-term efficacy of tetrabenazine, Kazamatsuri was unable to demonstrate lasting suppression of dyskinesic symptoms in 66% of the patients following 18 weeks of treatment. The initial suppression achieved with 100 mg per day did not persist in spite of doubling the dosage in the latter phases of the study.⁵³

Based on these studies, the clinical use of tetrabenazine does not look promising, since it has been shown not to have a prolonged therapeutic effect. In addition, possible long-term adverse effects of

the drug are unknown. Tetrabenazine is not marketed in the United States and is rarely used in pharmacotherapy of psychiatric patients even in the countries where the drug is available.

Methyldopa. This antihypertensive agent has been tried in the treatment of TD based on its ability to decrease dopamine activity via inhibition of dopa-decarboxylase. In an open study, Villeneuve noted some benefit from methyldopa in two of three patients receiving 750 to 1000 mg per day.⁴⁸

On the other hand, Kazamatsuri concluded that methyldopa has, at best, a barely perceptible effect on the abnormal movements of TD.⁵⁴ Comparing oral movements in nine patients during control and treatment periods, he observed a trend toward improvement in oral movements following one week of methyldopa treatment (1000 mg/day). This marginal therapeutic response, however, virtually disappeared in the second week. Side effects included a significant decrease in mean systolic pressure in the fifth and sixth week of therapy. Other adverse effects, including impotence in males, may limit the use of this drug in the long-term treatment of TD.

Dopamine Blocking Agents

Phenothiazines. Since TD is apparently related to dopamine receptor hypersensitivity, reestablishment of a high degree of dopamine receptor blockade will ameliorate the symptoms. Consequently, any dopamine blocking agent may mask the symptoms of TD. Thiopropazate, a phenothiazine used experimentally for the treatment of TD, will be discussed to exemplify the effect of these drugs.

Five studies utilizing thiopropazate in 37 patients demonstrated a mean improvement rate in 72% (range: 45% to 100%) of the patients.^{55,59} Kazamatsuri found that by adjusting the daily maintenance dose to less than 45 mg per day, the incidence of extrapyramidal symptoms was drastically reduced, while the suppression of dyskinetic symptoms was maintained.⁵⁸ Even though the majority of these studies were well controlled, the clinical efficacy of thiopropazate over long periods of time is not completely established and needs further investigation.

Haloperidol. Short and long-term studies have attempted to demonstrate haloperidol's efficacy in treating TD. Following four weeks of treatment in patients receiving up to 16 mg per day, 64% showed a reduction in oral movements.⁵⁸ However, in a long-term study involving seven patients, only 29% had complete disappearance of symptoms and two patients dropped out because of severe malaise.⁶⁰

Although the phenothiazines and other dopamine blocking agents, such as haloperidol, may be effective in attenuating the symptoms of TD, their use for this purpose raises a serious question. These agents do not cure the syndrome, but merely mask the symptoms. It is obvious that if the etiology of TD is chronic dopamine blockade, then

long-term treatment of the condition with a dopamine blocking agent is likely to further aggravate the underlying pathology. Except in patients requiring dopamine blocking drugs for control of otherwise unmanageable psychotic behavior, the use of these agents in patients with TD should be avoided.

Papaverine. Recently, Gardos and Cole⁶¹ suggested that papaverine, which has been found to antagonize dopamine in the caudate nucleus of the rat,⁶² may be useful for persistent dyskinesia in patients who have hypersensitivity to nigro-striatal dopamine. Results in three patients following three weeks of papaverine administration (300-600 mg/day) were as follows: in case I, the buccolingual dyskinesia tended to improve; in case II, the buccolingual dyskinesia improved whereas the rocking and choreoathetoid movements did not; and in case III, there was a tendency for all types of abnormal movements to improve. There were no apparent side effects of the drug in any subject.

The beneficial effects of papaverine may have been due to either the inhibitory effects on the dopamine pathways or the possible influence of cerebral vasodilatation. The authors concluded that until placebo controlled studies with larger samples confirm the preliminary findings, the value of papaverine in the treatment of TD remains speculative.⁶¹

Cholinomimetics

If TD is indeed due to an imbalance between the dopaminergic and cholinergic systems, then elevation in cholinergic tone may be useful in the treatment of this syndrome. Conversely, suppression of cholinergic tone may exacerbate the symptoms of TD. Therefore, the use of anticholinergic drugs, such as benztropine, trihexiphenidyl, biperiden, etc., is not a rational approach in the therapy of TD.^{40,42-44}

Dimethylaminoethanol. Based on the assumption that dimethylaminoethanol (deanol) is converted to acetylcholine in the brain,⁶³ investigators have attempted to treat TD with this drug.

Various reports have demonstrated sporadic improvement of abnormal movements in 0% to 100% of patients following one to five weeks of deanol therapy using doses ranging from 300 mg to 2000 mg per day.⁶³⁻⁶⁷ Only one investigator studied the effects of the drug for a longer period, and he found continued improvement at daily dosages of 1600 mg after two months.⁶⁴

Crane⁶⁶ and Davis *et al*⁶⁷ noted no improvement at one week when administering deanol in dosages of 1200 mg to 1600 mg per day, respectively. After three weeks of therapy, Crane noted marginal improvement in only 18% of his patients. Davis continued to observe no improvement for an additional two weeks despite increasing the dose to 2000 mg per day. Contrary to these relative failures, Miller⁶³ and Casey⁶⁴ noted total improvement in all three

patients receiving deanol at similar dosages.

It is unclear why some studies revealed favorable response to deanol while others did not. It is possible that TD is a heterogeneous condition and not all patients would be expected to respond to deanol. Crane offered a possible explanation for his poor findings. He speculated that previous successful trials using deanol may have included patients who have not had a long history of TD as was seen in his subjects.⁶⁶ This implies that deanol may not be effective in the latter stages of the disease.

Another explanation for the lack of success with deanol might be the underestimation of maximum doses required for improvement.⁶⁸ Granacher and Baldessarini, who are presently evaluating the pharmacotherapy of TD, found that clinical responses to deanol varied greatly. Some patients responded favorably only at doses greater than 2000 mg per day.³⁵

Choline. A recent case report utilizing choline chloride stemmed from the failure of deanol to reduce abnormal movements. A patient whose TD appeared to respond well to pretreatment cholinergic stimulation with physostigmine, failed to respond to deanol (2000 mg/day). This patient subsequently responded to large doses (16 gm/day) of choline chloride, a cholinergic stimulant. Even though the patient experienced sweating and salivation, the authors suggested this agent may be of some value in the symptomatic relief of chronic TD.⁶⁷

Other Methods of Treatment

There have been many drugs and treatment measures other than those previously mentioned which have shown some positive response in reducing the abnormal movements of TD. Operative procedures include stereotaxic neurosurgery.⁴⁷ Adjunctive correction of poorly fitting dentures has reduced oral movements in edentulous patients.^{7,69} Other drug therapy includes the use of monoamine oxidase inhibitors,⁷⁰ lithium carbonate,⁷¹ and combinations of dopamine depleting and blocking agents.⁷² No specific treatment, however, has been uniformly successful in alleviating the symptoms of TD.

PREVENTIVE MEASURES

Several measures can be taken to minimize the occurrence of TD.

1. Antipsychotic agents are seldom indicated as the initial approach to pharmacotherapy of non-psychotic patients with tension or anxiety. Severely anxious or agitated patients who do not respond to conventional therapy may be candidates for a trial on antipsychotic drugs, but only after careful consideration of the risk of TD.
2. In patients requiring chronic antipsychotic therapy, the dose should be titrated to the lowest possible level that provides adequate control.

Where it will not adversely affect a patient's attitude toward compliance, drug holidays may be employed.

3. Patients receiving antipsychotic drugs should be examined regularly for the appearance of the early signs of emerging TD: fine vermicular worm-like movements of the tongue and circular movements of the big toe. If such signs appear, the drug should be discontinued and the potential risks of TD be weighed against the necessity of continued drug administration.
4. The patient and/or his family should be informed of the risk of TD prior to institution of therapy. In view of prevailing legal predilections, it may be desirable to have a written record of informed consent.

CONCLUSION

Despite the apparent effectiveness of some drugs in the treatment of TD, it should be kept in mind that most of these studies involved a small number of patients. Because dyskinesias have been reported to subside in some cases after a few weeks or months,⁷³ the possibility of spontaneous remission as a confounding factor in studies without placebo controls cannot be eliminated.

It is evident that extended studies using reliable objective methods of assessment (i.e., cinematography, videotape and electrokinetography) are necessary to confirm or disprove the effectiveness of those drugs utilized to treat TD. Until an effective mode of therapy is found, the rational use of antipsychotic drugs in an attempt to prevent the occurrence of TD should be incorporated into each practitioner's prescribing habits.

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Continued on Page 135

Before prescribing, please consult complete product information, a summary of which follows:

Indications: In adults, urinary tract infections complicated by pain (primarily pyelonephritis, pyelitis and cystitis) due to susceptible organisms (usually *E. coli*, *Klebsiella-Aerobacter*, *Staphylococcus aureus*, *Proteus mirabilis*, and, less frequently, *Proteus vulgaris*) in the absence of obstructive uropathy or foreign bodies. **Note:** Carefully coordinate *in vitro* sulfonamide sensitivity tests with bacteriologic and clinical response; add aminobenzoic acid to follow-up culture media. The increasing frequency of resistant organisms limits the usefulness of antibacterials including sulfonamides. Measure sulfonamide blood levels as variations may occur; 20 mg/100 ml should be maximum total level.

Contraindications: Children below age 12; sulfonamide hypersensitivity; pregnancy at term and during nursing period; because Azo Gantanol contains phenazopyridine hydrochloride it is contraindicated in glomerulonephritis, severe hepatitis, uremia, and pyelonephritis of pregnancy with G.I. disturbances.

Warnings: Safety during pregnancy not established. Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been reported and early clinical signs (sore throat, fever, pallor, purpura or jaundice) may indicate serious blood disorders. Frequent CBC and urinalysis with microscopic examination are recommended during sulfonamide therapy.

Precautions: Use cautiously in patients with impaired renal or hepatic function, severe allergy, bronchial asthma; in glucose-6-phosphate dehydrogenase-deficient individuals in whom dose-related hemolysis may occur. Maintain adequate fluid intake to prevent crystalluria and stone formation.

Adverse Reactions: *Blood dyscrasias* (agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia); *allergic reactions* (erythema multiforme, skin eruptions, Stevens-Johnson syndrome, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis); *G.I. reactions* (nausea, emesis, abdominal pains, hepatitis, diarrhea, anorexia, pancreatitis and stomatitis); *CNS reactions* (headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo and insomnia); *miscellaneous reactions* (drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L.E. phenomenon). Due to certain chemical similarities with some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia. Cross-sensitivity with these agents may exist.

Dosage: Azo Gantanol is intended for the acute, painful phase of urinary tract infections. *Usual adult dosage:* 2 Gm (4 tabs) initially, then 1 Gm (2 tabs) B I D. for up to 3 days. If pain persists, causes other than infection should be sought. After relief of pain has been obtained, continued treatment with Gantanol (sulfamethoxazole) may be considered.

NOTE: Patients should be told that the orange-red dye (phenazopyridine HCl) will color the urine.

Supplied: Tablets, red, film-coated, each containing 0.5 Gm sulfamethoxazole and 100 mg phenazopyridine HCl—bottles of 100 and 500.



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SUDDEN INFANT DEATH SYNDROME IN MAINE — *Continued from Page 128*

been under the regular care of a physician, and the physician may have been contacted by the family regarding the above symptoms prior to the child's death. Interest has been expressed recently in doing more specific research on SIDS in Maine.

The program itself has specific parameters. The Medical Examiner is to submit a report within 72 hours to the Chief Medical Examiner, and the public health nurse is expected to contact the family as soon as possible. Table 2 shows how these factors appear for 1975.

Although 42 SIDS cases were reported in 1975,

the total number of SIDS which occurred is really unknown. The Division staff has not reviewed death certificates to determine unreported SIDS cases.

The SIDS Program managed by the Division of Public Health Nursing has had support from the Chief Medical Examiner, Charles F. Branch, M.D., from the Maine Chapter of the National Foundation of Sudden Infant Death Syndrome, from local nursing agencies, and from physicians and families.

From the Secretary's Notebook

Summary of 1975 Fall Meeting of the M.M.A. House of Delegates December 13, 1975 at Waterville, Maine

The Fall Meeting of the M.M.A. House of Delegates was held at the Mid-Maine Medical Center in Waterville on Saturday, December 13, 1975, with an attendance of 48 delegates and alternates and three guests. Euclid M. Hanbury, Jr., M.D., President of the M.M.A., called the meeting to order, and George W. Bostwick, M.D., Speaker of the House presided.

1. Dr. H. Alan Hume, Director of the **Emergency Medical Services Program** in Maine briefly explained the law and the grant given to the State, and how it will run. Material on the program will be going to hospitals in the State in January, to be followed by on-site visits, then a Statewide meeting the end of January.

2. Dr. Maurice Ross, Chairman of the M.M.A. Committee on Maternal & Child Welfare presented a **resolution** on the **EPSDT Program** which was amended and *approved* as follows:

WHEREAS, the Maine Medical Association House of Delegates, since June 1974, has adopted resolutions in favor of data continuity of medical care for children and warning against the possible fragmentation of such care in publicly supported child care programs;

WHEREAS, fragmented care generates unnecessary referrals and burdensome paper work and erodes the personal relationship between physician and family;

WHEREAS a greater involvement of the private physician in the ever expanding community health services is the only guarantee for competent professional standards therein;

WHEREAS, the State of Maine Department of Human Services has indicated its support of the above concepts in Title XIX Maine Medical Assistance Manual, Chapter V (Draft copy: September 1, 1975);

THEREFORE BE IT RESOLVED, that the Maine Medical Association endorses the goals and objectives of the EPSDT Program; and, BE IT THEREFORE FURTHER RESOLVED, that the Maine Medical Association urges the Department of Human Services or appropriate delegate to send a copy of the newly revised Chapter V,

Title XIX, Maine Medical Assistance Manual to each physician with an accompanying letter similar to the one attached to this resolution to determine how much each physician can support the EPSDT Program; and, BE IT THEREFORE FURTHER RESOLVED, that any agency to which the Department of Human Services will delegate any responsibility for screening of children under the EPSDT Program have a medical director or advisor with an interest in child care and development.

3. Dr. Francis Kittredge, our representative on the **Medical Malpractice Commission**, reported on its meetings and noted that public hearings will be held on January 16th in Presque Isle and January 17th in Bangor. Interested persons who wish to speak may apply to be heard. Public hearings in other parts of the State will be held later — 30 day notice will appear in local newspapers.

4. Dr. Richard T. Chamberlin, Chairman of the Executive Committee reported that on the recommendation of the sub-committee on insurance, the Committee on Health Care Financing and the M.M.A. Executive Committee voted to upgrade our **Group BCBS policy** to include major medical. This will go into effect on February 1, 1976, and all current subscribers will receive written notification of this later in December.

5. Committee Reports:

a) *Diabetes* — A copy of Chairman Melvin Bacon's report was given to each delegate. *No action.*

b) *Continuing Education* — Dr. Richard Chamberlin, Chairman, reported that the only requirement for membership in 1976 is that physicians report their CME activity — there are no specific number of hours required. The Committee is now discussing requirement of hours for 1977.

c) *Peer Review* — Dr. Chamberlin, Chairman, presented the question of how PTO (Maine's PSRO) relates to the M.M.A. as a source of peer review. This was discussed with the Executive Committee at a recent meeting and procedures are being worked on now.

6. *Report of AMA Clinical Convention* — Dr. Robert E. McAfee, our delegate to the AMA reported on this session held in Hawaii. Among items discussed were Health Systems Agencies, cata-

strophic illness, National Health Insurance, strikes, accreditation policy, malpractice, tobacco subsidies, air bags in vehicles, internal re-organization of the AMA, and continuing education. Keep up to date via the AMA News suggested Dr. McAfee, and if you have any questions, get in touch with him directly.

7. Other —

a) Dr. Hanbury explained the background on the **Health Systems Agency** and its development in getting organized in the State. He reported on the meeting of the selection committee and how the Board of Directors were chosen. Unhappy with much of the process thus far, Dr. Hanbury said that a letter is being prepared to go to the Commissioner of the Department of Human Services, which will objectively cite deficiencies in the development and selection process. It is felt that the law is difficult and can't work, and that it will be minimally funded.

Dr. Hanley added that this law will determine direction and assignment of every Federal dollar coming into Maine. The Secretary of HEW may develop and promulgate any regulation he so desires, they can decide where a doctor will or will not practice, and will decide on new buildings, new services, etc.

There are three M.D.'s on the Board of Direc-

tors of the HSA, but some areas are not represented, Dr. Hanley added.

b) A **resolution on direct billing** from Dr. Benoit Ouellette was referred to the April meeting of the House of Delegates.

c) Franklin County Medical Society has a **resolution regarding the Diabetes Detection Program** to be presented at the April meeting of the House of Delegates, about the desirability of spending \$1,000 of M.M.A. funds for this program.

d) Dr. McAfee reported recent changes under **Medicaid** — after January 1st, physicians will be asked to bill the absent parent, and the State will guarantee payment if the physician can't collect.

e) The question of the M.M.A. printing a **newsletter** was brought up again, and the Speaker of the House reminded the delegates that the Executive Committee considered this earlier and decided it was too expensive and time consuming.

8. **Spring Meeting of the House of Delegates** — Saturday, April 3, 1976 in Bangor at 2:00 P.M. (meeting of the Executive Committee at 10:00 A.M.)

9. Adjourned at 4:00 P.M.

PATRICIA A. BERGERON
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Program – 123rd Annual Session

Maine Medical Association

June 5, 6, 7, 8, 1976

Treadway-Samoset, Rockport

Arranged by the Scientific Committee

ROBERT H. PAWLE, M.D., Falmouth
Chairman

GEORGE E. DAVIS, M.D., Lewiston

The Scientific Program of the annual meeting of the Maine Medical Association is made possible by the cooperation and assistance of the Technical Exhibitors and the following organizations:

Maine Medical Center, Departments of Rheumatology, Orthopedics, Obstetrics-Gynecology and Pediatrics
Portland, Maine

Tufts University School of Medicine
Boston, Massachusetts

Merck Sharp & Dohme Postgraduate Program
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Maine Chapter, American Academy of Family Physicians

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Maine Society of Internal Medicine and the American College of Physicians

Maine Neurological Society

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Maine Radiological Society

Section on Ophthalmology of the M.M.A.

Otolaryngology Section of the M.M.A.

For this cooperation and support, the members of the Scientific Committee are grateful.

Information

Registration:

Registration throughout the session will be in the Lobby at the Treadway-Samoset.

Saturday, June 5 — 12:00 M. to 5:00 P.M.

Sunday, June 6 — 8:30 A.M. to 5:00 P.M.

Monday, June 7 — 8:30 A.M. to 5:00 P.M.

Tuesday, June 8 — 8:30 A.M. to 3:00 P.M.

Telephone: The number at the Treadway-Samoset is Rockport, (207) 594-2511.

Visiting Delegates:

Introduction of Visiting Delegates will take place at meetings of the House of Delegates on Saturday, June 5 and Sunday, June 6.

Technical Exhibits:

This year, sixteen companies are contributing to the success of the annual session program by participating in the Technical Exhibits. A list of the exhibiting companies and representatives will be found on pages 143 and 144.

Please show your appreciation for the support of these companies by visiting these exhibits.

Badge Code:

Badges with green borders indicate Officers, Past Presidents, Delegates and Alternate Delegates of the M.M.A.; yellow borders, members of the M.M.A.; blue borders, guests; red borders, exhibitors; and plain white for the members of the Auxiliary.

Saturday, June 5

2:00 P.M. First Meeting of the House of Delegates

Call to Order: EUCLID M. HANBURY, JR., M.D., President

Presiding: Speaker of the House, GEORGE W. BOSTWICK, M.D.

Presentation of the A. H. Robins' Physician Award for Community Service

Presentation of the Maine Blue Cross and Blue Shield "Award of Appreciation"

7:30 P.M. Dinner

Sunday, June 6

8:30 A.M. Reference Committee Meetings

12:30 P.M. Luncheon

2:00 P.M. Second Meeting of the House of Delegates

Election of President-elect and Executive Committee District Members

7:30 P.M. Dinner

Monday, June 7

Scientific Program

9:00 A.M. to 12:00 M.

Welcome — ROBERT H. PAWLE, M.D.

Presented by the Department of Rheumatology
Maine Medical Center, Portland

"ALL YOU NEED TO KNOW ABOUT RHEUMATISM"

Moderator — ALBERT ARANSON, M.D.

9:00 to 9:10 A.M. PHILIP P. THOMPSON, JR., M.D.

"Commiserate and Cop Out" or "Cure the Common Miseries"

The recognition and therapy of such common problems as "wryneck," trigger finger, tennis elbow, bursitis, night cramps and Morton's toe.

9:10 to 9:20 A.M. GEORGE L. MORTON, M.D.

"R. D. in P. D.'s"

The common manifestations of rheumatism in the child. Special emphasis will be placed on Juvenile Rheumatoid Arthritis vs. Rheumatic Fever, Dermatomyositis and Arthralgia of Rubella and Australian Antigen Hepatitis.

9:20 to 9:30 A.M. LARRY G. ANDERSON, M.D.

"Old Women's Pain in the Neck — Polymyalgia Rheumatica"

The presenting symptoms and complications of this frequent disorder of older people; its diagnosis and management.

9:30 to 9:40 A.M. ROBERT A. SYLVESTER, M.D.

"Life and Death Decisions in Rheumatology"

Rheumatic Diseases present as several emergent situations that should be recognized and acted upon quickly in order to prevent loss of life or loss of vital organs.

9:40 to 9:50 A.M. PAULDING PHELPS, M.D.

"What About . . . Gout?"

The use of polarized microscopy in the diagnosis and a plan for managing the various types of gout.

9:50 to 10:00 A.M. CURRIER McEWEN, M.D.

"A Pain in the Neck . . . An Aching Back!!!"

The recognition and management of varieties of persons, problems and "diseases" leading to an aching back will be condensed. Its essence will be capsuled by the wisdom of Dr. McEwen.

10:00 to 10:30 A.M. PANEL DISCUSSION

"How Rheumatologists Treat Rheumatoid Arthritis"

The diagnostic tests of importance, the message to give the patient, the order in which medications are used and indications for switching; the prescription to the therapists and useful aids in the home will be presented by the Rheumatology Department of the Maine Medical Center. Questions and answers by participants.

10:30 to 10:50 A.M. INTERMISSION

Presented by the Department of Orthopedics
Maine Medical Center, Portland

"ORTHOPEDIC CONTRIBUTIONS TO MANAGEMENT OF ACES, PAINS AND DEFORMITIES"

Moderator — LAWRENCE CRANE, M.D.

10:50 to 11:00 A.M. PATRICK A. DOWLING, M.D.

"Arthroscopy"

11:00 to 11:10 A.M. JOHN A. GODSOE, M.D.

"Surgical Procedures — Knee"

11:10 to 11:20 A.M. LAWRENCE M. LEONARD, M.D.

"Surgical Procedures of the Hip"

11:20 to 11:30 A.M. DONALD E. ALLEN, M.D.

"Surgical Procedures of the Hand"

11:30 to 12:00 M. PANEL DISCUSSION

"Practical Points in the Management of Musculo-skeletal Disorders"

Questions and answers by participants.

12:00 M. to 2:00 P.M. LUNCHEON

visit the technical exhibits

BEFORE AND AFTER EACH
SESSION AND DURING INTERMISSIONS

Scientific Program

2:00 to 4:00 P.M.

**Presented by the Departments of
Obstetrics-Gynecology and Pediatrics
Maine Medical Center, Portland**

"THE HIGH RISK MOTHER AND CHILD"

A combined presentation of the problem of the identification and management of the high risk obstetrical patient and the high risk neonate. The obstetrical, medical and social factors that contribute to fetal and neonatal morbidity and mortality will be discussed. The State of Maine statistics will be presented along with a description of the operation and statistics of the Maine Medical Center Neonatal Intensive Care Unit. An organized Statewide approach to continuing education and regionalization in obstetrics and current fetology will be presented.

Moderator — DOUGLASS W. WALKER, M.D.

2:00 to 2:25 P.M. HARRY W. BENNETT, JR., M.D.

Definition of high risk-incidence and screening questionnaire. Antepartum evaluation — past obs history, medical diseases, genetics, fetal evaluation, estriols, ultrasound, OCT, amniocentesis.

2:25 to 2:40 P.M. DAVID D. YOUNGS, M.D.

Social and dermatographic factors associated with high risk pregnancy, teenage pregnancy.

2:40 to 2:55 P.M. DONALD J. MCCRANN, JR., M.D.

Intrapartum evaluation of the fetus (Hobel Statistics). Fetal monitoring, intrauterine resuscitation, the cost of intrapartum asphyxia and prematurity.

2:55 to 3:15 P.M. JOHN C. SERRAGE, M.D.

The high risk neonate — recognition, treatment and transfer. Statistics of Maine Medical Center NICU.

3:15 to 3:30 P.M. ALBERT W. DIBBINS, M.D.

Team approach to the surgical management of the neonate.

3:30 to 3:45 P.M. DONALD J. MCCRANN, JR., M.D.

A Statewide approach to management of the high risk mother and fetus. ACOG statistics, regional planning, two-way referral.

3:45 to 4:00 P.M. PANEL DISCUSSION

Questions and answers by participants.

7:00 P.M. **Annual Banquet**

Presentation of Honorary Pins

President's Address: EUCLID M. HANBURY, JR., M.D.

The Robert Collier Chorale

Tuesday, June 8

Scientific Program

9:00 A.M. to 12:00 M.

Welcome — GEORGE E. DAVIS, M.D.

**Presented by Tufts University
School of Medicine, Boston**

"GASTROENTEROLOGY"

9:00 to 9:50 A.M. LON E. CURTIS, M.D., Associate Professor of Surgery, Tufts University School of Medicine; Senior Surgeon, New England Medical Center Hospital

"Evaluation of the Patient With Abdominal Pain"

9:50 to 11:10 A.M. LON E. CURTIS, M.D. and MARSHALL M. KAPLAN, M.D., Professor of Medicine, Tufts University School of Medicine; Chief of Gastroenterology, New England Medical Center Hospital

"Management of Peptic Ulcer Disease"

(There will be a 20 minute coffee break during this session)

11:10 to 12:00 M. MARSHALL M. KAPLAN, M.D.

"Hepatitis Update"

12:00 M. to 2:00 P.M. LUNCHEON

Scientific Program

2:00 to 3:50 P.M.

**Presented by Tufts University
School of Medicine, Boston**

"PULMONARY DISEASE"

2:00 to 2:50 P.M. GUSTAVE LAURENZI, M.D., Associate Professor of Medicine, Tufts University School of Medicine; Director, Department of Pulmonary Disease, Newton-Wellesley Hospital

"Pulmonary Infections 1976"

3:00 to 3:50 P.M. JOHN S. URBANETTI, M.D., Assistant Professor of Medicine, Tufts University School of Medicine; Assistant Physician, New England Medical Center Hospital

"Pulmonary Embolism: Ephemeral Events of Enigmatic Ideology"

Specialty Group Meetings

Monday, June 7

9:30 A.M. MAINE CHAPTER, AMERICAN ACADEMY OF PEDIATRICS

GEORGE W. HALLETT, M.D., Portland, presiding
Business Meeting

12:30 P.M. See "SPECIAL NOTICES" for Informal Luncheon Meetings of Specialty Groups on this page — upper right hand column.

2:00 P.M. MAINE SOCIETY OF INTERNAL MEDICINE AND THE AMERICAN COLLEGE OF PHYSICIANS

JOSEPH J. HIEBEL, M.D., Waterville and PHILIP P. THOMPSON, JR., M.D., Portland, presiding
Business Meeting

2:00 P.M. OTOLARYNGOLOGY SECTION OF THE M.M.A.

LORING W. PRATT, M.D., Waterville, presiding
"Soft Tissue Trauma of the Head and Neck"
JEROME GOLDSTEIN, M.D., Professor of Otolaryngology, Albany Medical College, Albany, New York

4:00 P.M. MAINE NEUROLOGICAL SOCIETY

KARL E. SANZENBACHER, M.D., President, Waterville, presiding
Business Meeting

Maine Medico-Legal Society

Tuesday, June 8

2:00 to 4:00 P.M.

Presiding — GEORGE O. CHASE, M.D., President, Bangor

"RAPE: ITS MEDICAL, LEGAL AND SOCIAL IMPLICATIONS"

Speakers:

MS. FRAN HARRIMAN, Scarborough, Maine
STANLEY W. KENT, M.D., Portland, Maine
SUSAN KOMINSKY, Esq., Bangor, Maine

This program sponsored by Dahl-Chase Pathology Associates and is acceptable for 2 hours credit in A.M.A. Category I for Physicians Recognition Award.

Special Notices

A.A.F.P. Prescribed Credit

This program is accepted for 8 Prescribed Hours by the American Academy of Family Physicians.

M.M.A. Credit for Category I

The Monday and Tuesday regular scientific sessions are accepted for 10 hours credit (1 credit per hour) in the Physicians Recognition Award Category I.

Informal Luncheons

Council of the Maine Society of Internal Medicine and the American College of Physicians — Monday, June 7.

Maine Society for Gastroenterology — Monday, June 7.

Maine Academy of Orthopedic Surgeons — Monday, June 7.

Otolaryngology Section of the M.M.A. — Monday, June 7.

Honorary Pins

Presentation of the Association's Honorary Pins will be made by Euclid M. Hanbury, Jr., M.D., President of the M.M.A., at the Annual Banquet, Monday evening, June 7 at 7:00 P.M.

FIFTY-YEAR PINS

Fifty-Year Pins will be presented to the following members who were graduated from Medical School in 1926.

Androscoggin County

Carleton H. Rand, M.D.
Tufts University School of Medicine

Cumberland County

Oscar R. Johnson, M.D.
Yale University School of Medicine

Kennebec County

Frank B. Bull, M.D.
University of Toronto Faculty of Medicine

Matthias Marquardt, M.D.
Chicago Medical School University of Health Sciences

M. Tieche Shelton, M.D.
Johns Hopkins University Medical College

Penobscot County

Carl E. Blaisdell, M.D.
Tufts University School of Medicine

FIFTY-FIVE-YEAR PINS

Fifty-Five-Year Pins will be presented to the following members who were graduated from Medical School in 1921.

Cumberland County

Edward Blumberg, M.D.
University of Leipzig Faculty of Medicine, Saxony

Oxford County
Henry M. Howard, M.D.
Bowdoin Medical School

SIXTY-YEAR PINS

Sixty-Year Pins will be presented to the following members who were graduated from Medical School in 1916.

Cumberland County
George O. Cummings, Sr., M.D.
Bowdoin Medical School

Herman C. Petterson, M.D.
Hahnemann Medical College

Somerset County
Maurice E. Lord, M.D.
University of Vermont College of Medicine

SIXTY-FIVE-YEAR PINS

Sixty-Five-Year Pins will be presented to the following members who were graduated from Medical School in 1911.

Cumberland County
James Patterson, M.D.
Rush Medical College

Knox County
Fred G. Campbell, M.D.
Baltimore Medical College

Piscataquis County
Edwin T. Wyman, M.D.
Tufts University School of Medicine

27th Annual Meeting

Auxiliary to the
Maine Medical Association
Open to All Physicians' Wives

Monday, June 7

Co-Hostesses: Lincoln-Sagadahoc, York Counties

9:00 A.M. to 12:00 M. Registration
Lobby, Treadway-Samoset, Rockport

9:30 to 10:15 A.M. Open House Coffee
Boutique II
Hostess: MRS. WILLIAM BUELL, President, York
County Auxiliary

10:15 A.M. House of Delegates Annual
Business Meeting — Installation
Boutique II
MRS. ROBERT F. FICKER, President, presiding

12:00 to 12:30 P.M. Reception Honoring
Communications
Pen-Bay Room

12:30 P.M. Annual Luncheon
Pen-Bay Room

MRS. ROBERT F. FICKER, presiding

Welcome — MRS. RICHARD C. LECK, Convention
Hostess

Invocation — REVEREND ROBERT HOWES

Forecast — RICHARD C. LECK, M.D., President-
elect M.M.A.

Guest Speakers — MR. RAY GEIGER and MR. KEN
CONNOR, Editors, Farmers Almanac

2:00 P.M. Adjournment

2:15 P.M. 1976-1977 Board of Directors Meeting
Pen-Bay Room

"Medicine Avenue"

Technical Exhibits

**Abbott Laboratories, North Chicago, Illinois
60064**

Representatives: Mr. William A. Towne, Mr. Bruce
Reynolds, Mr. Gerald J. Butts and Mr. R. Reilly

**Boehringer Ingelheim Ltd., 33 W. Tarrytown Rd.,
Elmsford, New York 10523**

**Bristol Laboratories, P. O. Box 657, Syracuse, New
York 03201**

**Burroughs Wellcome Co., 3030 Cornwallis Rd.,
Research Triangle Park, North Carolina 27709**

**Doyle's Office Equipment, Inc., R.F.D. #2, Gor-
ham, Maine 04038**

Representatives: Mr. Sidney M. Doyle, Jr. and Mr.
Steven M. Doyle

**E. F. Hutton and Company, Inc., 477 Congress St.,
Portland, Maine 04102**

**Lederle Laboratories, Pearl River, New York
10965**

**Maine Blue Cross and Blue Shield, 110 Free St.,
Portland, Maine 04101**

Representatives: Laura Franciose, R.N. and Mrs.
Shirley Brochu

**McNeil Laboratories, Inc., Camp Hill Rd., Fort
Washington, Pennsylvania 19034**

Representative: Mr. Joe Ruest

**Parke-Davis & Co., Joseph Campau at the River,
Box 118-General Post Office, Detroit, Michigan
48232**

Representatives: Mr. Gene Giroux and Ms. GERAL-
dine Schneider

**Pfizer Laboratories Division, 230 Brighton Rd.,
Clifton, New Jersey 07012**

**A. H. Robins Company, 1407 Cummings Dr.,
Richmond, Virginia 23220**

Representative: Mr. Albert W. Messer

Roche Laboratories, Nutley, New Jersey 07110
Representatives: Mr. Bill Cummings, Mr. Peter Davis, Mr. Jim DeVere and Mr. John Kane

Ross Laboratories, 625 Cleveland Ave., Columbus, Ohio 43216

Sandoz Pharmaceuticals, E. Hanover, New Jersey 07936
Representative: Mr. Larry Emidy

Searle Laboratories, Box 5110, Chicago, Illinois 60680
Representatives: Mr. Daniel Arimento, Mr. Alfred Grimes and Mr. Thomas Ordway

Visiting Delegates

The Connecticut State Medical Society
BERNARD O. NEMOITIN, M.D., Stamford

The Massachusetts Medical Society
RUSSELL J. ROWELL, M.D., Beverly

Medical Society of the State of New York
RALPH S. EMERSON, M.D., Lake Success

The Rhode Island Medical Society
RUSSELL P. HAGER, M.D., Warwick

Vermont State Medical Society
HARRY M. ROWE, M.D., Wells River

Delegates to Out-of-State Meetings

The Connecticut State Medical Society
RICHARD M. SWENGEL, M.D., Lewiston

The Massachusetts Medical Society
JOHN B. MADIGAN, M.D., Houlton

New Hampshire Medical Society
DONALD L. ANDERSON, M.D., Lewiston

Medical Society of the State of New York
EUCLID M. HANBURY, JR., M.D., Belfast

The Rhode Island Medical Society
LEONARD G. MIRAGLIUOLO, M.D., Bangor

Vermont State Medical Society
ROBERT F. FICKER, M.D., Kennebunkport

County Delegates

DELEGATES

ALTERNATES

Androscoggin County Medical Association

Richard M. Swengel, M.D., Secretary	
Charles A. Hannigan, M.D.	Margaret H. Hannigan, M.D.
Stanley D. Rosenblatt, M.D.	Jon P. Pitman, M.D.
Thomas F. Shields, M.D.	Richard W. Turcotte, M.D.
Jou S. Tchao, M.D.	Kenneth P. Wolf, M.D.
Behzad Fakhery, M.D.	Mary T. Dycio, M.D.

Aroostook County Medical Society

George J. Harrison, M.D., Secretary	
Rodrigue J. Albert, M.D.	Michael J. Kellum, M.D.
Eric F. Nicholas, M.D.	William A. O'Brien, M.D.
Madjid Yaghmai, M.D.	Arthur D. Pendleton, M.D.

Cumberland County Medical Society

Wesley J. English, M.D., Secretary	
Robert W. Agan, M.D.	Louis A. Ciampi, M.D.
John R. Davy, M.D.	Patrick A. Dowling, M.D.
Carl S. Jackson, M.D.	Andrew P. Iverson, Jr., M.D.
Frederick S. Larned, M.D.	John D. Kilgallen, M.D.
Stuart W. McGuire, M.D.	Thomas A. Martin, Jr., M.D.
Robert H. Pawle, M.D.	Irving J. Poliner, M.D.
David L. Adams, M.D.	Martin A. Barron, Jr., M.D.
Donald P. Cole, M.D.	William J. Hall, III, M.D.
Bernard Givertz, M.D.	Theodore J. Hallee, M.D.
Walter H. Goldfarb, M.D.	John E. Knowles, M.D.
William L. MacVane, Jr., M.D.	Bruce D. Nelson, M.D.
Stephen E. Monaghan, M.D.	Alfred E. Swett, M.D.
	Stanley B. Sylvester, M.D.

Franklin County Medical Society

Daniel K. Onion, M.D., Secretary	
Paul A. Brinkman, M.D.	David C. Dixon, M.D.

Hancock County Medical Society

(No delegates appointed)

Kennebec County Medical Association

Oscar T. Feagin, M.D., Secretary	
Howard H. Milliken, M.D.	Antoine A. Atallah, M.D.
Anthony Betts, M.D.	J. Alfred Letourneau, M.D.
Raymond E. Culver, M.D.	Harry M. K. Peddie, M.D.
Earle M. Davis, M.D.	John H. Shaw, M.D.
George I. Gould, M.D.	Charles E. Towne, M.D.

DELEGATES

ALTERNATES

Terrance J. Sheehan, M.D.	Ulrich B. Jacobsohn, M.D.
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Knox County Medical Society

David G. Reed, M.D., Secretary	
Christopher F. Manning, M.D.	Robert J. Dreher, M.D.
	Peter R. Shrier, M.D.

Lincoln-Sagadahoc County Medical Society

George W. Bostwick, M.D., Secretary	
Anthony J. Hortsman, M.D.	Frank O. Avantaggio, Jr., M.D.
David W. Schall, M.D.	Gilbert R. Rowan, M.D.

Oxford County Medical Society

Kenneth G. Hamilton, M.D.	James A. Edmond, M.D.
David L. Phillips, M.D.	Robert W. Scarlata, M.D.

Penobscot County Medical Society

Philip G. Hunter, M.D., Secretary	
John J. Pearson, M.D.	William M. Blackwell, M.D.
Robert P. Andrews, M.D.	Jack N. Meltzer, M.D.
Francis I. Kittredge, M.D.	David S. Beebe, M.D.
John A. Ordway, M.D.	Roy S. Patten, M.D.
Lewis E. Phillips, M.D.	James R. Curtis, M.D.
Leonardo L. Leonidas, M.D.	A. Dewey Richards, M.D.

Piscataquis County Medical Society

Charles H. Stone, III, M.D., Secretary

Somerset County Medical Society

John H. Steeves, M.D., Secretary	
Harland G. Turner, M.D.	Richard C. Taylor, M.D.

Waldo County Medical Society

Joseph A. Smith, M.D., Secretary	
Harold E. Knuuti, M.D.	T. Craig Childs, M.D.

Washington County Medical Society

Karl V. Larson, M.D., Secretary	
Robert G. MacBride, M.D.	Donald M. Robertson, M.D.

York County Medical Society

Melvin Bacon, M.D., Secretary	
William O. Buell, M.D.	Lawrence R. Hazzard, M.D.
Carl E. Richards, M.D.	Marcel P. Houle, M.D.
Michael M. P. Magaudo, M.D.	G. Patrick Shaw, M.D.



Maine Blue Cross and Blue Shield News

Service Benefits and Major Medical

Our Professional Relations representatives receive many questions from participating physicians regarding Blue Shield coverage. In this column we will attempt to answer those that deal with broad policy questions and that would seem to be of interest to most physicians' offices. We would welcome any suggestions for questions you would like to see addressed in this space.

A question frequently asked is why the service benefit provision contained in all the Blue Shield contracts applies if the subscriber also has major medical coverage.

The Blue Shield contracts contain a statement that "any member is automatically removed from the Service Benefit classification: . . . When the member receives from another source additional benefits to which he is legally entitled for the same or similar services. . . ." Thus, the service benefit provision does not apply if the subscriber has additional *basic* health insurance.

The Blue Alliance Major Medical policy, however, is written expressly as *supplement* to basic Blue Shield. It provides benefits *after* the policyholder has exhausted his basic coverage and met an out-of-pocket deductible. Because one of the basic Blue Shield benefits is the service benefit provision, Blue Alliance policy-holders are not covered for balances remaining after Blue Shield payments have been made if they are eligible for service benefit under their Blue Shield contracts.

The question is sometimes expressed in the following way: "If the subscriber is eligible for Blue Alliance Major Medical benefits, why can't we bill him for the balance?" The answer is that the service benefit subscriber is in fact not eligible for Major Medical benefits because the Blue Shield contract is primary and the Blue Alliance contract does not come into effect until the terms of the Blue Shield contract have been satisfied.

What Is Blue Alliance?

The Blue Alliance Mutual Insurance Company was formed to provide major medical and extended benefits only with Maine Blue Cross and Blue Shield coverage, and Maine Blue Cross and Blue Shield is administrative agent for Blue Alliance.

Originally, Maine Blue Cross and Blue Shield had wanted to provide extended benefits in addition to Blue Cross and Blue Shield as part of the non-profit corporation, but a 1965 Supreme Court ruling held that the legislature did not have the right to grant privileges under special law that were not granted in the public law which governs non-profit hospital and medical service corporations. The court held that there was not a discernible difference between the Extended Benefits Program contract and commercial contracts and, therefore, it would not apply under the non-profit hospital and medical service organization Legislation.

In 1966, certain Maine Blue Cross and Blue Shield staff and Board members elected to establish a separate insurance company through which the supplemental benefits Maine Blue Cross and Blue Shield was legally unable to underwrite could be offered.

So the Blue Alliance Mutual Insurance Company operates solely for the purpose of providing additional benefits after both the Blue Cross and Blue Shield contractual terms have been satisfied.

County Society Notes

York

The combined meeting of the York County Medical Society and its Auxiliary was held on January 7, 1976 at the Cascades Inn in Saco, Maine.

The program was as follows: Social Hour from 6:30 to 7:30 p.m., Dinner at 7:30 p.m., Speaker, business meeting and dancing followed.

The speaker was Eddie Mayo of Kennebunkport, Maine, an artist of wide renown. His subject concerned the Kennebunkport Dump Association. This talk was most interesting, entertaining and replete with humor.

One of the highlights of this meeting was the election of Dr. Owen O. Dow of Kennebunk, Maine to the Presidency of the York County Medical Society. He is a Mainer by birth. His elementary school was spent in Saco, Maine and Hopedale, Massachusetts and he is a graduate of Dartmouth College with an A.B. Degree. In addition, he is a graduate of Tufts University School of Medicine in 1964. From 1964 to 1965, he was an intern at the Maine Medical Center and was a resident in general surgery at this Institution from 1965 to 1969. Certified by the American Board of Surgery in 1970, he became a Fellow of the American College of Surgeons in 1972. He is a member of the staff at the Webber Hospital, Biddeford and the Maine Medical Center, Portland. In addition, he was engaged in the practice of general surgery in Narragansett, Rhode Island from 1969 to 1971 and in Saco from 1971 to present.

The following is a list of the officers and committees elected:

President: Dr. Owen O. Dow, Kennebunk

Vice-President: Dr. Ralph S. Belmont, Sanford

Secretary-Treasurer: Dr. Melvin Bacon, Sanford

Executive Committee: Drs. Walter R. Peterlein, Springvale, Robert S. Lafond, Saco, Owen O. Dow, Ralph S. Belmont and Melvin Bacon

Delegates to the M.M.A. House of Delegates: Drs. Carl E. Richards, Sanford, William O. Buell, Biddeford and Michael M. P. Magaouda, Old Orchard Beach

Alternates: Drs. Marcel P. Houle, Biddeford, Lawrence R. Hazzard, York and G. Patrick Shaw, Biddeford

Censors Committee: Drs. Marion K. Moulton, Chairman, West Newfield, Roger J. P. Robert, Biddeford and Paul S. Hill, Jr., Saco

Peer Review Committee: Drs. Kenneth E. Leigh, Chairman, York, Harry Lapirow, Kennebunk and Conner M. Moore, Saco

Nominating Committee (1977): Drs. Melvin Bacon, Chairman, John H. Leonard, York and Andre P. Fortier, Biddeford

Executive Committee of the M.M.A., 1st District, York Co.: Dr. Maurice Ross, Saco

Another feature of this meeting was the introduction of Mrs. William Buell, President of the York County Medical Society Auxiliary, who also was in charge of the guest list, and other prominent guests by Dr. Carl Richards, outgoing President of the Society, who also presided over the business meeting. Dr. Richards was elected to his 34th term as a delegate to the Maine Medical Association. A brief financial report was given. The minutes of the last meeting were dispensed with in the interest of time. All members were urged to send in their forms to the Maine Medical Association concerning their Postgraduate Education.

All those physicians in York County who are not members of the York County Medical Society were urged to join. Dr. Richards spoke at length about the House of Delegates meeting of the Maine Medical Association held in December 1975 at the Thayer Hospital in Waterville. He reported on malpractice insurance and the increase in Blue Cross-Blue Shield coverage. He also brought out that each county society would be requested to decide how many credits from Category I would be necessary to meet the educational requirements of the Maine Medical Association. It was suggested if anyone has any ideas on the subject to write to Dr. Bacon. Mention was made of the report of Dr. Robert E. McAfee, delegate of the Maine Medical Association

to the American Medical Association; he stated that it is possible that the Health Service Agency of which there is one in Maine could be unconstitutional, that the American Medical Association is against compulsory health insurance plans and favor a privately funded plan mostly for catastrophic illnesses. They are against striking but you can do it if you wish. They also favor the Joint Commission having one set of standards for hospital accreditation.

A resolution about sick physicians was also mentioned. The American Medical Association is treading water on Malpractice Insurance. One of its major issues concerns internal reorganization of its staff.

Dr. Richards also mentioned a resolution on Diabetes brought up by the Franklin County Medical Society which although not voted in will be brought up in the future. The ADC (Aid to Dependent Children) issue was also discussed.

A subject which also evoked much explanation and is one which was open for criticism was the Health Systems Agency which is to replace the Hill-Burton and Regional Health Care.

A resolution submitted by Dr. Ross and passed by the group was discussed at length by Dr. Ross. Our president stated that Dr. Ross and Dr. Bacon also attended this meeting of the House of Delegates. He also announced the next meeting of the York County Medical Society would be held at the Goodall Hospital, Sanford, Maine on Wednesday, March 10, 1976. The Committee in charge of arrangements for this meeting consists of Drs. Carl Richards and Melvin Bacon. The remainder of the meetings for the rest of the year were also announced and are as follows: May 12, 1976 — Webber Hospital, Biddeford, Maine; October 13, 1976 — York Hospital, York, Maine; January 12, 1977 — Location to be announced later.

Dancing followed the business meeting, but because of the inclement weather it was decided to curtail the dancing and head for home. There were approximately 50 physicians, wives and guests present. Mention should be made that the music for dancing was furnished by Syd Lerman and his Orchestra.

MELVIN BACON, M.D., *Secretary*

Penobscot

The monthly meeting of the Penobscot County Medical Society was held on January 20, 1976 at the Holiday Inn East, Bangor, Maine.

The meeting was opened by the President, Dr. Thornton W. Merriam, Jr., who then introduced several guests in attendance.

The minutes of the December 1975 meeting were read and approved.

A resolution on the death of Dr. Hans Weisz was then presented by Dr. Frederick C. Emery. The resolution becomes part of the permanent record of the County Medical Society, and a copy of the resolution will be forwarded to Mrs. Weisz.

Several communications were received during the course of the previous month. All communications were in response to letters sent from the Society as directed by the December 1975 meeting. The first communication was received from Governor James Longley in response to our protest of the method of selection of the Board of Directors of the Maine Health Systems Agency. The second communication was received from Commissioner David Smith of the Department of Human Services who responded to the Society's objection to the requirement placed upon physicians treating AFDC children to seek a financially responsible parent prior to State reimbursement. The third communication was received from Dr. Bradley Brownlow who had been appointed a member of the Board of Directors of the Health Systems Agency who responded to our letter encouraging his active participation in this organization.

Applications for membership into the County Medical Society were received from Drs. Robert Gause and Dan Mayer. Dr. Gause was unanimously approved for active membership of the Society, and Dr. Mayer was unanimously approved to junior membership of the Society.

Following the business meeting, a panel discussion on the subject of Medical Malpractice was then begun. Dr. John Woodcock, moderator of the panel, provided opening remarks and introduced panel members. These included lawyers Errol Paine and Kevin Cutty and physician Dr. Francis I. Kittredge. Each member of the panel made an introductory statement which was followed by a lively and open question and answer session between the panel members and the floor. Mr. Paine, as a plaintiff's attorney and Mr. Cutty as a defense attorney provided interesting insight into the nature of their profession and their own thinking with regard to the conduct of medical malpractice and its potential litigation.

As there was no further business, the meeting was adjourned.
PHILIP G. HUNTER, M.D., Secretary

Cumberland

The 400th monthly meeting of the Cumberland County Medical Society was held on January 15, 1976 at the Unionmutual Building on Outer Congress Street with the social hour beginning at 6:30 p.m. This was the annual member-spouse night and 241 members and spouses were present.

After a delicious buffet dinner, the President, Dr. Robert E. McAfee, introduced Mrs. Eleanor Lovely who encouraged participation and help from the C.C.M.S. members at the time of the annual book sale. Dr. McAfee then introduced all of the past presidents of the C.C.M.S., reminiscing about their years in office.

The main program for the evening was the introduction of the "Physician of the Year." Dr. McAfee, in his humorous fashion, told of the difficulties encountered by the selection committee in choosing a physician for the award. Then to the surprise and delight of all present, he announced that 14 C.C.M.S. physicians were finally selected for the award, all of them women. The following were the recipients of the award: Drs. Mary E. Fenn, Anneliese M. Andrews, Marjorie A. Boyd, Sara K. Cope, Gisela K. Davidson, Carmel L. Davy, Frances M. Dyro, Carolina I. Haverty, Gloria M. Miniutti, Alice H. Parsons, Elizabeth G. Serrage, Nina B. Rubins, Alice A. S. Whittier and Doris S. Pennoyer.

Each recipient was introduced by a C.C.M.S. member familiar with her many accomplishments, some of which were summarized and each recipient received a bicentennial medallion (provided by Dr. William L. MacVane, Chairman of the Portland Bicentennial Committee), a corsage and a certificate indicating her selection as "Physician of the Year."

The meeting was adjourned at 10:30 p.m.

WESLEY J. ENGLISH, M.D., Secretary

Lincoln-Sagadahoc

The regular monthly meeting of the Lincoln-Sagadahoc County Medical Society was held on January 20, 1976 at The Ledges in Wiscasset, Maine. There were twenty-four members and guests present.

The meeting was called to order at 8:35 p.m. by the Vice-President, Dr. Anthony J. Horstman. After dinner, the minutes of the December meeting were read by the Secretary and accepted as read.

Dr. Richard C. Leck reported, for Old Business, that the M.M.A. Search Committee is still entertaining applications for the position of Assistant to the Executive Director. He reported on further activities of the State Health Systems Agency. After a discussion, in which H.S.A. was vilified, Dr. Leck then mentioned provisions of H.R. 10284, which state that a PSRO organization can charge a hospital for its services, even in the absence of a Memorandum of Understanding.

Under New Business, Dr. Robert H. Dixon announced that the County Society Auxiliary has offered to help in political problems by appearing at legislative hearings in Augusta or helping solicit political support. Dr. Anthony J. Keating spoke in support of this role of the Auxiliary. He moved, and several seconded, that the Secretary write the Auxiliary thanking its members for this expression of support. The motion was passed.

Dr. Bostwick read the 1975 Report of the Treasurer; it was accepted as inevitable.

Dr. Horstman introduced the chairman of the Scientific Committee, Dr. Dixon, who spoke on "Nosebleed." He showed many charts to illustrate pathology and treatment.

The regular monthly meeting of the Lincoln-Sagadahoc County Medical Society was held at The Ledges in Wiscasset, Maine on February 17, 1976. There were twenty-seven members and guests present.

The meeting was called to order after dinner at 8:38 p.m. by the President, Dr. David S. Hill. The minutes of the January meeting were read and accepted as such.

The secretary then read correspondence:

1. a warning that Federal law S-2697 would fine physicians \$10,000 for prescribing drugs for indications not listed in package stuffers;

2. a letter from the State Superintendent of Insurance to M.M.A. warning of non-licensed status of "The Condor Trust" in soliciting malpractice insurance;

3. communications requesting for cooperation with State health nurses in conducting screening examinations of children under EPSDT. There was no objection to accept referrals of regular, or some new, patients for such screening;

4. an inquiry from Medical Care Development, Inc. about sponsorship of instructional meeting to discuss use of Physician Assistants. The members felt that this Society is too small to sponsor a meeting of such Statewide interest.

Dr. Richard C. Leck brought the membership up to date on the State Health Systems Planning Agency.

The Board of Censors proposed for active membership Dr. William G. Wilkoff of Bath; the nomination was accepted unanimously by those present.

Dr. Hill then introduced Dr. Raymond H. Dominici who spoke on "Peripheral Vascular Surgery" and showed interesting radiograms of aneurysms.

GEORGE W. BOSTWICK, M.D., Secretary

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**Paul A. Fichtner, M.D.
 Arlene V. Fichtner, R.N.**

Letters to the Editor

To the Editor:

Over the last two or three years you have been kind enough to accept information from Colby concerning the continuing medical education programs that we hold each summer. We do not yet have brochures printed for this summer, but we do have our schedule pretty well put together and brochures will be available over the next few weeks. We still have Category I accreditation through the AMA's Council on Medical Education. I might add that last summer was the best ever that Colby had with registrants from all fifty states, as well as most of the Canadian Provinces and a few foreign countries.

The American College of Physicians is again co-sponsoring Oncology/Hematology courses and the American Society of Hematology, and the American Association of Cancer Association are also co-sponsoring those two courses. The American Thoracic Society allows us the use of the double-barred cross for the Pulmonary Disease program, and we have had support from the Maine Law Enforcement and Planning and Assistance Agency for the Forensic Medicine program.

The seminars and institutes in chronological order that will be offered at Colby this summer are as follows: The 31st Annual Lancaster Course in Ophthalmology, June 12-August 20; Topics in Hematology/Oncology, July 11-18; Surgical Techniques and Problems, July 20-23; Advanced Seminar in Audiology, July 20-23; Seminar in Neurosurgical Techniques, July 25-29; Frederick T. Hill Seminar in Otolaryngology, August 1-5; Seminar in Ophthalmology, August 8-12; Seminar in Nuclear Medicine, August 16-20; Topics in Pulmonary Disease, August 22-26; Seminar in Forensic Medicine, August 22-26.

Your readers might wish to know that I am the coordinator for all of these programs and if there are any questions, they could be directed to me at Colby College, Waterville, Maine 04901.

If there is room to publish something about these courses in your publication, we of course appreciate it greatly. We do feel as if we have helped to contribute to medical education, not only for the State of Maine and the New England region, but for the entire country. Thanks again for all your help.

R. H. KANY
Director
Division of Special Programs
Colby College
Waterville, Maine 04901

To the Editor:

We are happy to announce, effective January 15, 1976, the Veterans Administration will pay for your services according to a new Schedule of Fees negotiated between the VA and the Maine Medical Association/Maine Osteopathic Association. Enclosed is a copy of the Medical Section of the new schedule, which covers the most common procedures. The conversion factor for this section is 10.* The Surgery, Radiology and Laboratory Sections are lengthy and are not being reproduced for distribution; however, we will gladly answer any questions you have regarding specific procedures in these sections. These fees represent the maximum allowable; you should charge the VA your usual and customary fee, and your invoice should include the statement that the fees charged are those charged the general public.

In order to facilitate prompt processing of your invoices, and eliminate the need to return them for clarification, please use the procedure code numbers and nomenclature listed in the enclosed section when billing for your services.* If you are billing for an electrocardiogram, please tell us whether it was a 9101, 9102 or 9103; if billing for an office visit, list one of the four codes from 9001 to 9005; if billing for psychiatric services, list psychotherapy codes according to time spent with the patient, etc.

Because we realize there is some confusion as to what constitutes an authorization from the VA to provide outpatient treatment at VA expense, we enclose an enlarged copy of the VA Outpatient Medical Treatment Information Card.* Without ex-

ception, any patient who is authorized outpatient treatment at VA expense will possess one of these cards. If the patient does not have one of these cards, the VA should not be made the responsible party for payment. Any questions the patient may have in this regard should be referred to the Fee Services Unit at this Center, telephone 623-8411, ext. 255.

\$40 MONTHLY LIMITATION

This card authorizes only \$40 for all combined treatment each month. If you know that treatment will exceed this limit, please make your recommendations to the Outpatient Service at this Center for approval. Failure to request prior approval may result in denial of payment over \$40 for that month.

PHYSICAL EXAMINATIONS

Complete, general, routine physical examinations are *NOT* authorized by this card. Initial examination of the patient is covered in procedure code 9001. Procedure codes 9081 and 9082 are used only for examinations specifically authorized by the VA for rating purposes. If you feel the veteran should have a complete examination, please make your recommendations to this Center.

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When writing prescriptions for disabilities approved by the card, please make this statement on the prescription: "I am authorized to treat and prescribe for the disability for which this prescription is written, by the VA," or use VA Prescription Form 10-2577b, available on request from this Center. If you are prescribing for a disability not covered by the card, please do not use the VA Prescription Form 10-2577b.

For complete information, please read the enclosed card carefully, noting its limitations.* This card authorized OUTPATIENT TREATMENT ONLY, and does not authorize any inpatient care. If hospitalization is required, please make your recommendations to the Admitting Office at this Center (you may call collect 623-8411, extension 252). Notice of a veteran's emergency admission to a private hospital should be made to the VA within 72 hours of admission if VA authorization for the care is desired. If the veteran is eligible, the VA can authorize payment until the veteran can be safely moved to an appropriate VA facility. If the veteran is not entitled to non-VA hospital care, then arrangements can be made to transfer him or her to a VA facility as soon as medically feasible and a bed is available.

Your acceptance of a patient as a veteran beneficiary presenting this card constitutes an agreement to treat the veteran within the limitations of the card, and accept payment according to the VA approved Schedule of Fees. The veteran should not be billed for any charge over and above VA payment for any particular service.

We hope this information is helpful to you. Please feel free to contact the Fee Services Unit, 623-8411, extension 255, at any time for further assistance.

EDWARD S. O'MEARA, M.D.
Chief, Outpatient Service
Veterans Administration Center
Togus, Maine 04330

*Copies mailed to physicians with letter

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Adenocarcinoma of the Cecum Initially Presenting With Vaginal Bleeding

JOHN ZERNER, M.D., FACOG, FACS,* ROBERT G. MACBRIDE, M.D.
and WALTER B. GOLDFARB, M.D., FACS**

It is known that the vagina may be involved secondarily by gynecological tumor and through direct extension of a non-gynecological malignancy.^{18,24} However, secondary involvement by a non-genital lesion, and not by direct extension, is rare.¹⁷ Accordingly, we present a case of metastatic adenocarcinoma to the vagina that was shown to be of cecal origin without direct communication from the primary site.

CASE REPORT

The patient, a 54-year-old, Gravida III, Para III, whose LMP occurred in 1972, was seen for yearly physical examination in January 1975. No abnormalities were noted, and pap smear was negative. In May of 1975, she complained of vaginal spotting of three weeks' duration. Prompt evaluation by her primary physician disclosed a 3 x 3 cm midline lesion involving the posterior upper one-third of the vagina. A pap smear taken of this area was interpreted as "adenocarcinoma with a question of ovarian origin."

The patient was admitted to the Maine Medical Center where laboratory studies showed an anemia with hematocrit of 30. Stool guaiac was negative. X-ray studies, including AP and left lateral of the chest, metastatic series, and upper GI and barium enema were all considered within normal limits. On 7/7/75 examination under anesthesia with fractional curettage, multiple cervical and vaginal biopsies, proctosigmoidoscopy and cystoscopy were performed. On bimanual examination the question of an adnexal mass on the left was noted. Laparoscopic examination showed an enlarged ovary on the left side measuring approximately 7 cm in diameter with the right ovary being grossly normal. The posterior cul-de-sac was clear of any abnormality. There was no seeding by tumor of the pelvic peritoneum. Biopsies were taken of the left ovary.

Pathology showed: 1) vaginal biopsy demonstrating well differentiated papillary mucous producing adenocarcinoma (Figure 1), 2) cervical biopsies exhibiting only mild dysplasia, 3) en-

dometrial curettings with a single focus of papillary hyperplasia.

The patient was then explored with the thought that perhaps ovarian carcinoma, as evidenced by the left adnexal mass, would be found along with metastatic spread to the vagina. However, at celiotomy a large tumor involving the cecum with invasion through the serosa as well as an apparent metastasis to the local lymph nodes was noted. Both ovaries were found to be involved with tumor. The pelvic peritoneum grossly was free of any malignancy. A right colectomy with ileotransversecolostomy and bilateral salpingo-oophorectomy was performed.

Pathology demonstrated: 1) well differentiated mucous producing adenocarcinoma of the cecum with two separate primaries (Figure 2), 2) both ovaries exhibiting a similar type of adenocarcinoma, 3) the left uterine tube having an intraluminal well differentiated mucous producing adenocarcinoma, 4) peritoneal washings positive for carcinoma.

Postoperatively the patient's hospital course was complicated by a wound infection, and with thrombophlebitis of the lower extremity for which the patient was anticoagulated successfully.

Upon discharge plans were made for initiation of chemotherapy (5-Fluorouracil) as well as radiotherapy at a later date.

DISCUSSION

The problem in deciding whether a vaginal malignancy is primary or metastatic is often a difficult one. At this point it is worthwhile to briefly mention some of the various malignancies with their characteristics that may appear in the vagina. Cervical squamous cell carcinoma can extend directly to the vagina. Extension to the vagina not only advances staging of the cervical lesion, but also decreases survival.²¹ Primary squamous cell carcinoma of the vagina, composing between 1 and 2 percent of all gynecological malignancies^{12,16,1} most commonly originates in the posterior upper one-third¹⁵ or the anterior lower one-third of the vagina.¹⁶ Interestingly, should tumor be found to involve both vagina and cervix, the lesion, by definition, must be considered a cervical primary with extension to the vagina. Hence, to prove the existence of a primary vaginal carcinoma, multiple cer-

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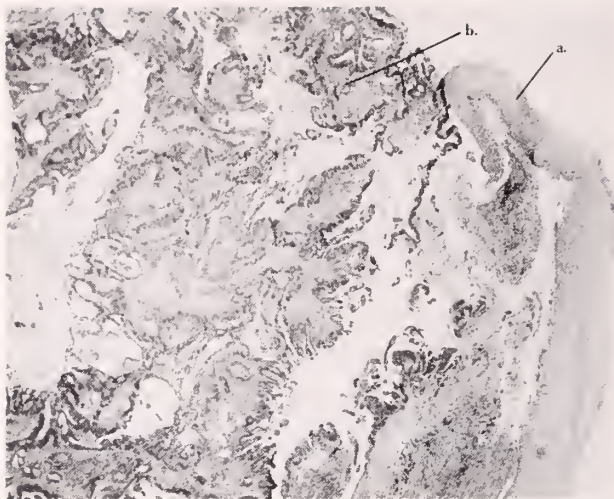


Fig. 1. Photomicrograph (100x) showing the vaginal lesion with normal vaginal mucosa (a) and metastatic adenocarcinoma (b).

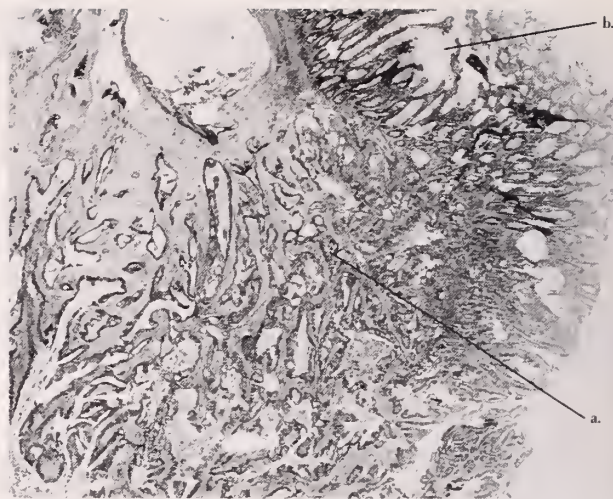


Fig. 2. View of the primary cecal lesion with tumor (a) and normal bowel mucosa (b) (100x).

vical biopsies must be taken to eliminate the latter as a site of initial involvement.^{9,18}

Although the overwhelming percentage of vaginal carcinomas microscopically will be of squamous cell type, approximately 5 percent (range 1-9 percent) are found to be adenocarcinomas.^{9,15} Due to the extreme rarity of vaginal adenocarcinoma, the physician must first exhaustively search for a primary lesion distant from the vagina.^{14,15} Most often the endometrium proves to be the site of origin.¹⁴ Endometrial metastases commonly present on the anterior vaginal wall, in a suburethral location. In addition, endometrial metastases involving the vaginal cuff have been noted in 12 to 16 percent of patients receiving no adjuvant therapy prior to, or following, surgery.^{13,20} The hypernephroma, or renal cell carcinoma, has been reported metastasizing to the vagina, most often from the left kidney and primarily to the anterior wall suburethrally. This particular predilection of left renal carcinoma spreading to the vagina is based on hematologic retrograde spread of tumor emboli to the pampiniform and ureterovaginal plexuses,²⁷ secondary to direct communication of the left renal and left ovarian vein.^{22,24}

Ovarian tumors may directly erode through the posterior vaginal wall and present as a fungating cauliflower lesion seen in the upper vagina.

Other rare malignancies but without specific findings that have metastasized to the vagina are those of the pancreas,²⁴ lymphatic system²² and melanomas.¹⁰

The remainder of the discussion will revolve around tumors of the large bowel. Colorectal tumors are the most common visceral carcinoma in the United States.¹ They are now the second most common mitotic lesion in the United States, exceeded only by those of the skin. These malignancies account for approximately 99,000 cases yearly and 49,000 deaths per year, which is the second

highest cause of death in the United States due to malignancy exceeded only by those of the lung.² Cecal tumors account for approximately 12-16 percent of all large bowel carcinomas.¹

Symptomatically, tumors of the left colon (descending colon, sigmoid and rectum) often present early in the course of the disease with acute hemorrhage and/or obstruction allowing for curative resection because of their limited spread. However, unlike the symptoms of the left colon, those of cecal tumors are insidious.²³ Patients may be treated for their symptoms in a variety of ways (i.e., high protein diet, iron, Vitamin B) only resulting in a delay of definitive diagnosis so that by the time the triad of 1) malaise and weight loss, 2) anemia, and 2) palpable mass is noted, the lesion is often so advanced that surgical intervention is palliative and not curative.^{1,7}

Large bowel carcinoma can extend to the vagina. Most commonly it is by geographic (i.e., direct) involvement and is especially seen in roughly 10 percent of those tumors of the sigmoid or rectum.³ Cecal tumor, because of its location at the pelvic brim, has rarely been reported to spread to the vagina by this direct manner without massive involvement of the entire abdominal cavity. It is known that spread of tumor may occur in one of four ways — direct extension, hematologic spread, implantation, and lymphatic spread with the first (direct extension) being the most common to the pelvis. Lymphatically, spread will be from local to distant nodes within the abdominal cavity.

The case reported is unique as vaginal presentation seems to have been in a way that could not be explained by direct extension, lymphatic spread or implantation. The more likely explanation involves the vertebral vein system, a set of valveless vessels carrying blood under low pressure. This system is constantly subject to arrest and reversal in the direction of flow of blood; it also parallels, connects

with, and provides bypasses for the portal, pulmonary and caval system of veins.³ Hence, these vessels can provide a pathway for the spread of tumor to remote organs such as the liver, lung, and brain.¹¹ Therefore, our patient's vaginal lesion could be explained by venous metastasis of the cecal carcinoma via retrograde flow through the vertebral systems, thence to the ovaries and finally to the vagina. Further, a case could be made here for the concept of "oviduct pickup" whereby malignant cells, shed by an abdominal lesion are engulfed by the amoebic action of a uterine tube and passed through its lumen into the endometrial cavity. From there, expulsion and possibly eventual implantation could take place in the vagina. Indeed, microscopic examination showed a discrete lesion in the lumen of the left uterine tube without any apparent serosal or muscularis involvement. Additionally, there was no pelvic peritoneal gross involvement that could account for a possible cul-de-sac lesion extending through the vaginal cell into the vagina itself.

Hence — what may be learned of this case? First, a metastatic lesion was found initially that led to the eventual discovery of the primary. Secondly, multiple biopsies must always be taken of any vaginal lesion and, if adenocarcinoma is found, the physician must look elsewhere for a primary. Thirdly, x-ray studies can, on occasion, show false or negative interpretations.⁷ This is especially true in the cecum because of 1) its large size and variable appearance, 2) predisposition for retained feces to localize in the cecum and 3) the overlapping of the rectosigmoid which may obscure this area.⁸ In general, the evaluation of each patient with vaginal neoplasm must be meticulous and methodical.²⁵ It is the responsibility of the physician to prove that this lesion is not metastatic, knowing the rarity of its occurrence. This is especially true of any lesion described as adenocarcinoma of the vagina.^{14,26} Naturally, the genital area must be evaluated with examination under anesthesia, fractional curettage, multiple cervical and vaginal biopsies (with laparoscopic examination of the pelvic contents if need be). The urinary system must also be completely studied through an IVP and cystoscopic examination. Thorough evaluation of the gastrointestinal tract with barium enema, upper GI series, proctosigmoidoscopy, and of course examination of the stool for occult blood is indicated. Further x-ray studies must also be obtained to rule out any extra abdominal spread as evidenced by chest x-rays and metastatic series. Any suspicious lesion found at these sites, we feel, may be indication for exploratory surgery in an attempt to ascertain whether primary tumor is present within the abdomen. Nothing could be worse than to treat a vaginal lesion as primary only to find at a later date that, indeed, this was metastatic and that the original tumor was located elsewhere.

SUMMARY

Several points ought to be emphasized 1) Vaginal bleeding in the postmenopausal female must be considered abnormal and evaluated promptly and thoroughly, 2) Any mass nodule or bleeding site must be biopsied, 3) Vaginal lesions, because of their rarity, must be proven to be primary of the vagina and not metastatic 4) Hence, evaluation of other systems must be performed prior to the initiation of any definitive therapy, 5) In spite of all these precautions, a patient may be treated with an incorrect diagnosis. Physicians must do all possible to prevent such an occurrence.

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Normal Pressure Hydrocephalus and Urinary Incontinence

WILLIAM H. LESCHEY, JR., M.D.* and ANDREW P. IVERSON, JR., M.D.**

A decade after publication of the original paper in 1965,¹ controversy over normal pressure hydrocephalus (NPH) continues. The large number of papers presenting different views reflects the commonness of dementia, and the frustrations of the physicians who deal with the demented patient. There is no agreement as to the definition of NPH,³ and some neurologists and neurosurgeons even question the existence of such an entity. Few authors have addressed the problem of urinary incontinence in NPH. Explanations for the urinary incontinence have varied from the lack of social inhibitions²⁹ to the presence of a neurogenic bladder.¹⁵

CASE REPORT

A. M., Mercy Hospital No. 243299, was admitted to the hospital on 11/14/74 for evaluation of ataxia, moderate dementia, and urinary incontinence. She had been incontinent of urine for approximately 2 and one-half years and in 1973 had had an anterior colporrhaphy which was unsuccessful. On admission, her residual urine was 50 cc after voiding approximately 150 cc. An intravenous pyelogram was obtained which revealed a question of a filling defect in the right renal pelvis. A voiding cystourethrogram revealed a trabeculated bladder with a residual urine again of approximately 50-75 cc. No vesicoureteral reflux was noted. A carbon dioxide cystometrogram was obtained using a flow rate of 120 cc per minute (Figure 1) which revealed a bladder capacity of approximately 100 cc. She was totally unable to inhibit the voiding reflex under a voiding detrusor pressure of almost 80 cm of water. When the study was repeated utilizing a flow rate of 60 cc per minute (Figure 2), again she had a bladder capacity of approximately 90 cc before she had the urge to void and was unable to inhibit adequately the voiding reflex. She did attempt to and was able to inhibit it just slightly. When the pelvic nerve was blocked with 50 mg of I.M. Bantline® (Figure 3), the patient had a bladder capacity of over 200 cc before the study was discontinued. At that time, she had no effective detrusor contractions illustrating that the patient had an uninhibited neurogenic bladder.

Neurologic examination revealed that the patient had a strongly positive bulbocavernosus reflex, marked ataxia, and was moderately demented. Other findings were that the patient showed extinction of any left-sided stimulus to bilateral simultaneous stimulation and the face-hand test was positive. She also had palmomental reflexes. Two point discrimination was also greatly impaired in the left hand and was normal in the right hand. Position sense was normal in the great toes bilaterally. No Babinski's were present. There was a mild decrease of the left ankle jerk as compared to the right. The patient was symmetrically ataxic. The initial neurologic impression was that this patient possibly had a focal process in the right cerebral hemisphere, and also the question of normal pressure hydrocephalus was raised.

Skull films were normal. A brain scan revealed findings consistent with dilated lateral ventricles. A right brachial arteriogram (Figures 5 and 6) was performed on 11/27/74 which suggested an enlarged ventricular system with no evidence of cortical atrophy.

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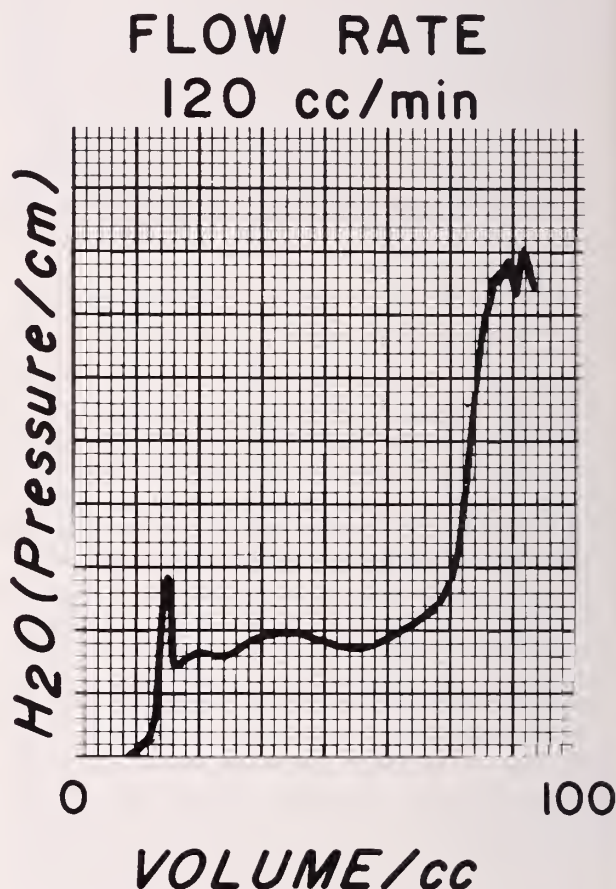


Fig. 1. CO₂ cystometrogram showing patient's inability to inhibit detrusor contraction at a volume of 90 cc.

On 11/29/74, a pneumoencephalogram was performed which revealed enormous lateral ventricles with minimal sulcal air (Figure 7). The third and fourth ventricles appeared normal. The frontal horns measured 40 mm in height with a cerebral mantle of 22 mm (Figure 8).

A cystoscopy revealed a very trabeculated bladder. A right retrograde pyelogram proved that the so-called filling defect on the IVP was merely an artifact. On 12/9/74, a ventriculoatrial shunt was performed by the neurosurgical service. The patient's postoperative course was uneventful. She became progressively more oriented mentally, and her gait markedly improved. Her urinary incontinence completely subsided, and she had a normal voiding schedule voiding 200-400 cc at a time. In August of 1975, a carbon dioxide cystometrogram was performed (Figure 4) which revealed normal sensory and motor parameters and the fact that she was able to inhibit her voiding reflex. Her bladder capacity also was normal for a woman of this age.

DISCUSSION

The concept of a communicating obstructive hydrocephalus is integral to most current theories concerning the pathogenesis of NPH. The block to

cerebrospinal fluid (CSF) flow is hypothesized as being at various sites external to the ventricular system. The block may be located in the basal cisterns, the incisura, the convexity subarachnoid spaces, the arachnoid villi, or any place between CSF output at the fourth ventricular foramina and absorption in the sagittal sinus. The end result is a dilated ventricular system that communicates with the subarachnoid space. The CSF pressure is normal, but a period of high pressure is postulated as preceding the normal pressure.¹² In the early papers, the authors theorized that maintenance of the expanded ventricular system was on the basis of Pascal's principle. The total force against the ventricular surface is greater because the surface area on which the pressure acts is greater. Later, factors operative within the brain substance were implicated in the pathogenesis.^{9,10}

The etiology is apparent in many cases, and includes subarachnoid hemorrhage, severe head injury, acute and especially chronic meningitis, meningeal carcinomatosis, certain neurosurgical procedures (following removal of posterior fossa tumors), parasagittal meningiomas, and a few other types of brain tumors which do not produce internal hydrocephalus. Ectasia or aneurysm of the basilar artery may produce incisural block and secondary occult hydrocephalus.⁶

When all these causes of NPH are excluded, a sizeable group of idiopathic cases remains. There is virtually no controversy about the secondary occult hydrocephalus group.^{24,27} These cases are better defined clinically, and there is agreement that improvement occurs in the majority after a shunting procedure.

Controversy, disagreement, and inconsistent

results are present in discussions centering on the idiopathic group. Much of the problem is that there is no generally accepted definition for NPH. Some authors define NPH on a clinical basis, and others rely on a certain laboratory test which incorporates an implied pathophysiologic theory. The fact is that neither the clinical symptoms and signs, nor any of the proposed laboratory tests provide a satisfactory definition of NPH. The cases within the idiopathic group that will improve with shunting cannot be identified by clinical or any presently available laboratory methods.^{14,27,31}

The classical triad of clinical findings consists of

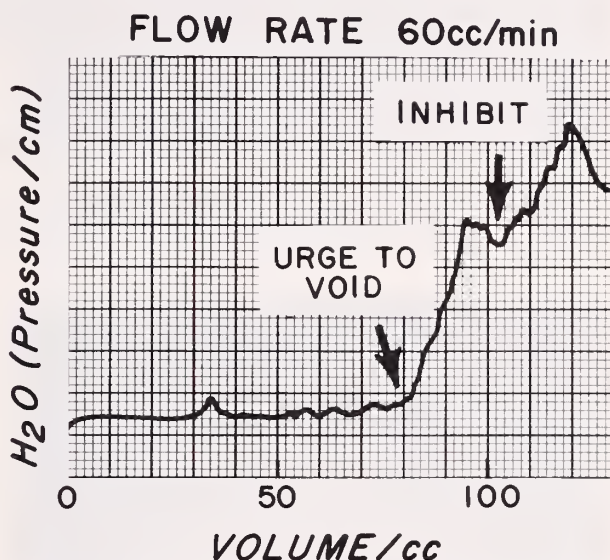


Fig. 2. When CO₂ cystometrogram was repeated at an infusion rate of 60 cc/min., the urge to void was noticed by the patient, but she again was unable to adequately inhibit the detrusor contraction.

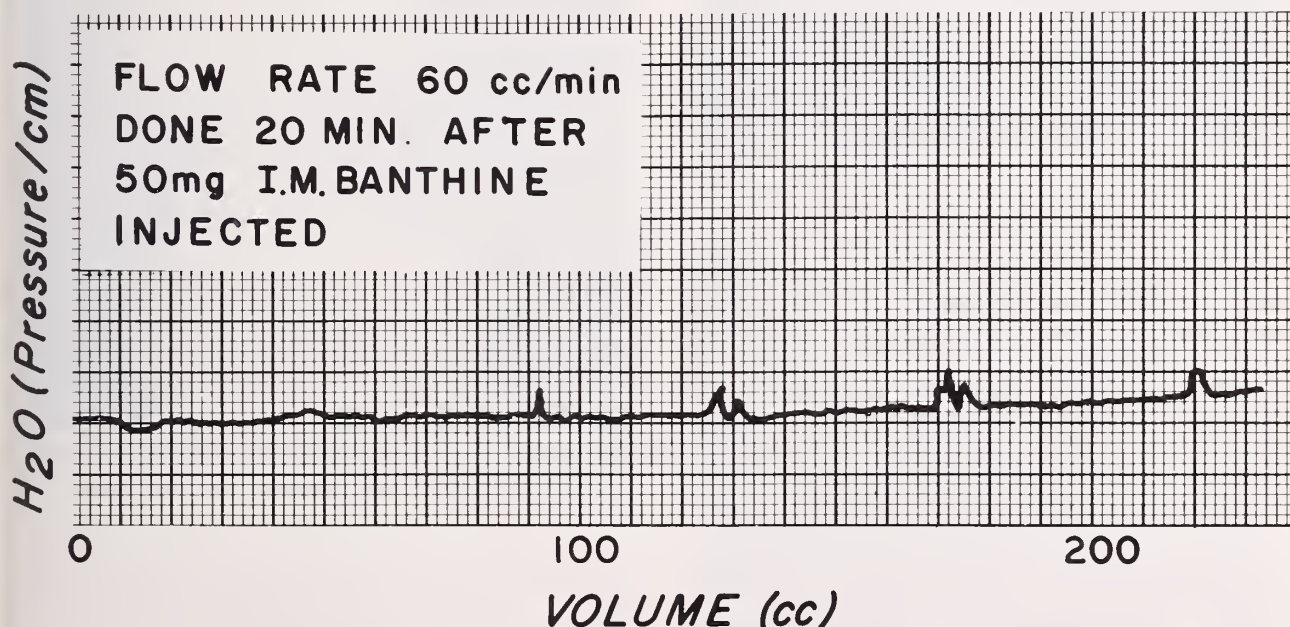


Fig. 3. When the pelvic nerve is blocked with IM Bantnine, the uninhibited detrusor contractions are abolished, illustrating an uninhibited neurogenic bladder.

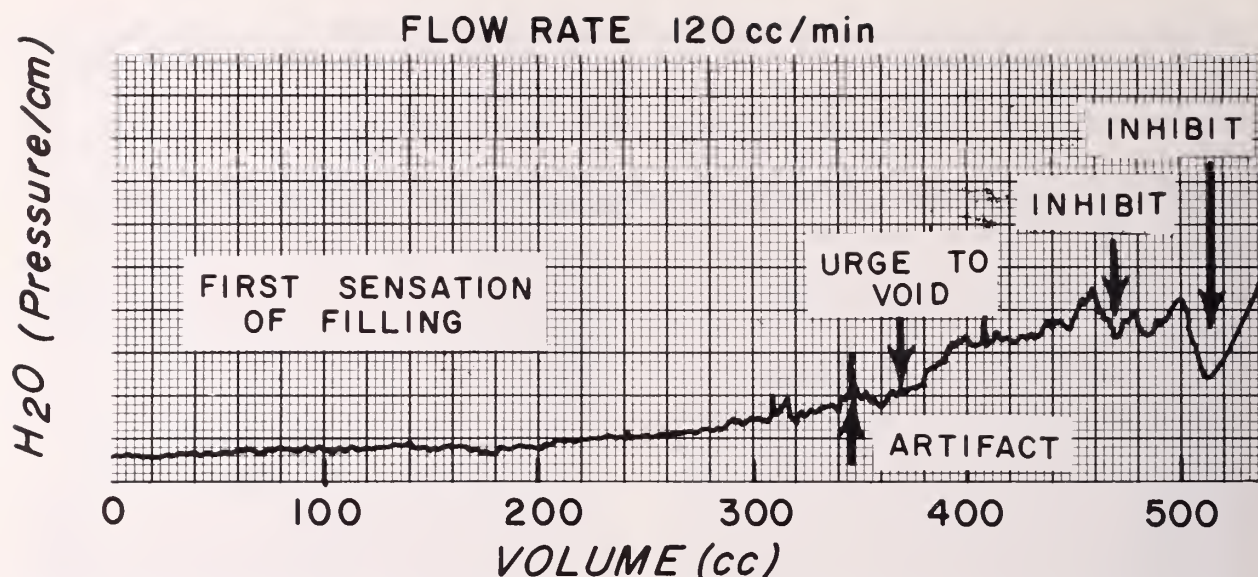


Fig. 4. CO₂ cystometrogram done after the ventriculoatrial shunt was performed, illustrating normal motor and sensory parameters, the ability to inhibit voluntarily the detrusor contractions, and that she now has a normal bladder capacity.



Fig. 5. Lateral view of right brachial arteriogram shows a stretched and elevated pericallosal artery.

dementia, gait disturbance, and urinary incontinence. Higher cortical deficits vary from severe dementia to a mild personality or affective disorder.⁴ Apathy and psychomotor retardation are often present. Memory impairment is usually demonstrable. Focal cortical deficits, such as anomia, aphasia, and agnosia are commonly absent, and are more suggestive of CNS degenerative or vascular disease. Mild dementia and short duration are said to be favorable with respect to prognosis following shunting.⁴ All types of motor disturbances have been described. *Gegenhalten* is often present in the limbs.²⁴ The findings may simulate hypokinetic parkinsonism, but resting tremor is not usual. The most characteristic gait is a magnetic or apractic



Fig. 6. Frontal projection, venous phase, of right brachial arteriogram shows marked lateral displacement of the thalamostriate vein.

one in which the patient has difficulty initiating lifting movements of the feet in spite of the absence of weakness. Patients with frontal lobe neoplastic or degenerative disease may manifest this same gait abnormality. A spastic paraparesis or quadriparesis

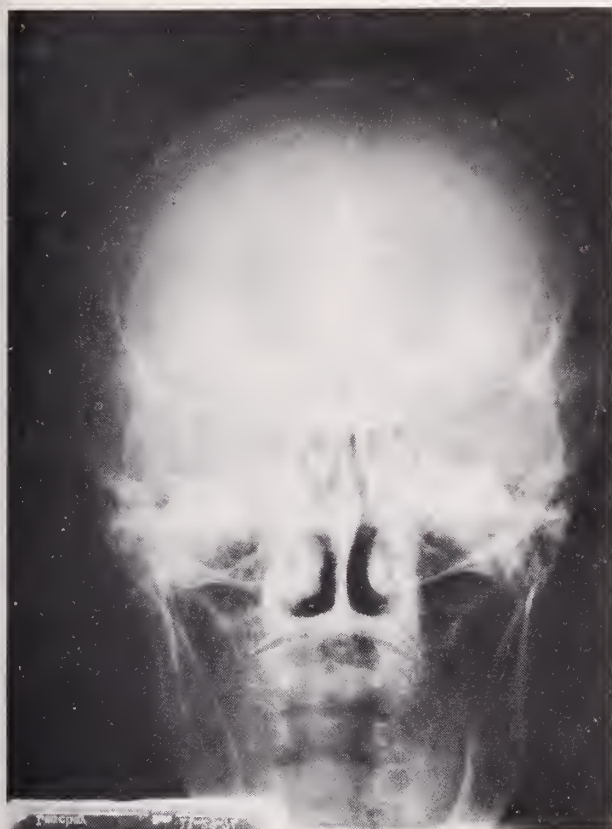


Fig. 7. AP view of air study reveals marked symmetrical dilatation of the lateral ventricles without evidence of cortical atrophy.

with extensor toe signs may also be seen in NPH. The presence of motor signs has been described as correlating with a favorable outcome after shunting.¹⁴ Urinary frequency, urgency, and incontinence are common, but not constant findings. A frontal lobe localization is often suggested by the clinical symptoms and signs. Sometimes, relatively specific frontal lobe release phenomena including snout, suck, and grasp reflexes are present.

The memory disturbance in hydrocephalus has been described as being mild, and characteristic of that found in frontal lobe disease.³⁰ Not infrequently, immediate recall (digit span), recent memory (3 objects after 3 minutes), and remote memory (personal and historical events prior to illness) are all intact. Nonetheless, family members relate behavioral evidence to suggest impaired memory functions. This frontal lobe memory disorder has been characterized as "forgetting to remember," and has been hypothesized as being a deficit in goal oriented behavior, and related to frontal lobe and limbic system disconnection.¹³ The hypokinesia and apathy in frontal lobe disease (and hydrocephalus) are similarly interpreted as defects in attention and arousal caused by frontal lobe-reticular formation disconnection.

The gait disturbance and lower extremity motor signs in hydrocephalus have for sometime been thought to relate to selective vulnerability of med-

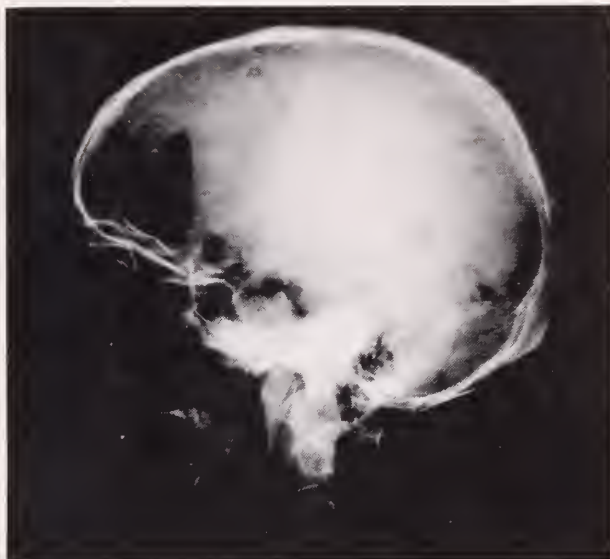


Fig. 8. Lateral view of pneumoencephalogram shows air in basilar cisterns, but not over hemispheres. The greatly enlarged frontal horns measure 40 mm in height with a cerebral mantle of 22 mm.

ically originating long tract fibers which course around dilated frontal horns.¹ Other fibers originating in medial frontal and cingulate areas, and destined for reticular formation and limbic structures may well be subject to the same forces.

A series of laboratory procedures have evolved in attempt to identify patients with NPH, and predict which cases would improve with shunting. The pneumoencephalogram was the test employed in the original study.¹ A symmetrically dilated ventricular system with incisural block, and absence of air over the cerebral hemispheres were described as the essential features. Many other air study criteria were subsequently published, and include a narrow callosal angle¹⁸ (less than 120 degrees), cerebral mantle measuring less than 40 millimeters,¹⁸ height of the frontal horn greater than 32 millimeters,¹⁸ increased ventricular size in 24 hour delayed films²⁶ (above 25 percent), increase in temporal horn width,²⁸ and worsening clinical status after the study. Complete absence of air over the cerebral hemispheres is no longer considered necessary for the diagnosis of NPH. Greater amounts of air over the hemispheres are now accepted as being consistent with NPH, if certain patterns such as convexity block are present,¹¹ and the sulci are not diffusely and significantly widened. The pneumoencephalogram remains useful in evaluating the NPH suspect, but will no doubt be employed less frequently when computerized tomography (CT) becomes more widely available as a screening test.

Cerebral angiography can provide clues to the diagnosis of NPH, but is no longer considered appropriate in the evaluation of an uncomplicated case of dementia.² Ventricular dilatation may be evident by bowing and upward displacement of the anterior cerebral artery on the lateral view, and

lateral displacement of the middle cerebral artery and thalamostriate vein on the anteroposterior views. In hydrocephalus of cerebral atrophy (hydrocephalus ex vacuo), a tortuous anterior cerebral artery is usually seen, and the lateral displacement of the thalamostriate vein is less in degree. More direct radiographic evidence of cortical atrophy is sometimes found.

Isotope cisternography was introduced in 1964, one year prior to publication of the original paper on NPH.⁸ This procedure discloses dynamic information about CSF flow, and the discovery of ventricular concentration of isotope in cases of communicating hydrocephalus seemed certain to provide a definitive test for NPH. Some investigators, in fact, considered persistent ventricular concentration as the basic definition of NPH, and argued that only cases fulfilling this criterion would improve with shunting.^{21,23} More recent studies, however, have suggested that isotope cisternography is not helpful in predicting improvement after shunting.^{14,27} Biopsy proven cases of Alzheimer's disease have been reported with a positive isotope cisternogram and failure to respond to shunting. In addition to persistent ventricular reflux, other various patterns are considered to be compatible with NPH, and include impaired convexity circulation, and failure of parasagittal isotopic accumulation. More recently, radionuclide blood levels during cisternography have been found to be diminished in NPH compared to patients with Alzheimer's disease, but again the data did not clearly differentiate which patients would improve with shunting.²⁰

A simple, but ingenious test called constant-infusion manometry was introduced in 1970.¹⁶ This procedure is based on the premise that patients with obstructed CSF flow would react differently than those with normal CSF dynamics to fluid injected into the lumbar subarachnoid space at a rate exceeding normal CSF production. A rapid rise in lumbar CSF pressure and the appearance of severe headache are described as indicating obstructive hydrocephalus. Although the procedure operates on an attractive pathophysiological principle, prediction of the successful shunt patient has been disappointing.³¹ Misleading results and failure to correlate with other studies may be related to faulty needle tip position, since there is no certain way to determine if the tip is properly located within the subarachnoid space.

When it became apparent that no one test could define the NPH patient that would improve with shunting, multiple criteria including both clinical and laboratory tests were advocated. One such scheme included the criterion of projected rhythmic frontal delta slowing on the electroencephalogram (EEG).²² Although the EEG in general reflects physiological parameters rather than static structural change, the usefulness in NPH has been lim-

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Before prescribing, please consult complete product information, a summary of which follows:

Indications: In adults, urinary tract infections complicated by pain (primarily pyelonephritis, pyelitis and cystitis) due to susceptible organisms (usually *E. coli*, *Klebsiella-Aerobacter*, *Staphylococcus aureus*, *Proteus mirabilis*, and, less frequently, *Proteus vulgaris*) in the absence of obstructive uropathy or foreign bodies.

Note: Carefully coordinate *in vitro* sulfonamide sensitivity tests with bacteriologic and clinical response; add aminobenzoic acid to follow-up culture media. The increasing frequency of resistant organisms limits the usefulness of antibacterials including sulfonamides. Measure sulfonamide blood levels as variations may occur; 20 mg/100 ml should be maximum total level.

Contraindications: Children below age 12; sulfonamide hypersensitivity; pregnancy at term and during nursing period; because Azo Gantanol contains phenazopyridine hydrochloride it is contraindicated in glomerulonephritis, severe hepatitis, uremia, and pyelonephritis of pregnancy with G.I. disturbances.

Warnings: Safety during pregnancy not established. Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been reported and early clinical signs (sore throat, fever, pallor, purpura or jaundice) may indicate serious blood disorders. Frequent CBC and urinalysis with microscopic examination are recommended during sulfonamide therapy.

Precautions: Use cautiously in patients with impaired renal or hepatic function, severe allergy, bronchial asthma; in glucose-6-phosphate dehydrogenase-deficient individuals in whom dose-related hemolysis may occur. Maintain adequate fluid intake to prevent crystalluria and stone formation.

Adverse Reactions: *Blood dyscrasias* (agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia); *allergic reactions* (erythema multiforme, skin eruptions, Stevens-Johnson syndrome, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis); *G.I. reactions* (nausea, emesis, abdominal pains, hepatitis, diarrhea, anorexia, pancreatitis and stomatitis); *CNS reactions* (headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo and insomnia); *miscellaneous reactions* (drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L.E. phenomenon). Due to certain chemical similarities with some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia. Cross-sensitivity with these agents may exist.

Dosage: Azo Gantanol is intended for the acute, painful phase of urinary tract infections. *Usual adult dosage:* 2 Gm (4 tabs) initially, then 1 Gm (2 tabs) B.I.D. for up to 3 days. If pain persists, causes other than infection should be sought. After relief of pain has been obtained, continued treatment with Gantanol (sulfamethoxazole) may be considered.

NOTE: Patients should be told that the orange-red dye (phenazopyridine HCl) will color the urine.

Supplied: Tablets, red, film-coated, each containing 0.5 Gm sulfamethoxazole and 100 mg phenazopyridine HCl—bottles of 100 and 500.



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ited. Focal slowing or a normal record were far more common findings than projected bifrontal slow activity in one series.⁷

Computerized tomography is the newest radiological procedure which has been employed in the investigation of patients with dementia. This technique using conventional x-ray and a computer to determine absorption values of the cranial contents provides visualization of the ventricular system and subarachnoid spaces. In patients with NPH, the typical pattern consists of generalized ventricular dilatation, and compressed subarachnoid spaces over the cerebral hemispheres. In contrast, patients with cerebral atrophy or primary CNS degenerative disease have scans with expanded subarachnoid spaces, and widened sulci, and only mild ventricular dilatation. The periventricular white matter in NPH may have decreased CT absorption values, possibly related to increased water content.²⁴ As the ventricles become smaller after shunting, the absorption values may revert to the normal white matter range. This non-invasive screening test may provide only limited structural information, which is independent of CSF dynamics; however, the previously described invasive studies do not appear to provide a practical answer as to which patients will improve with shunting. Therefore, CT scanning will no doubt assume more importance, and be increasingly employed in evaluation of the demented patient. Absolute magnitude of ventricular dilatation in absence of expanded subarachnoid spaces and sulci may be grossly determined by this technique, and ventricular size seems to be an important variable in determining success of shunting. A large number of patients showing significant cortical atrophy may be spared additional studies including potentially dangerous procedures. Cisternography, or some improved test of CSF dynamics will continue to be of use to demonstrate actual obstruction of CSF flow.

Cystometry, although a relatively old technique, has only recently been applied in the study of bladder function in NPH. More recent innovations in cystometrographic procedures include carbon dioxide insufflation with automatic recording, as employed in the patient presented. One series of five patients studied with a simple water manometer reported cystometrographic findings classified as uninhibited neurogenic bladder in three, an uninhibited neurogenic variant in one, and a mixed pattern in the remaining case with associated lower motor neuron involvement.¹⁵

Urinary continence is regulated by cerebral control over the detrusor muscle and periurethral striated muscles. The neuroanatomical substrate of micturition can be conceived as consisting of four neuronal circuits which function in an integrated fashion to determine detrusor and periurethral striated muscle output.⁵ The first circuit connects the frontal lobes to the pontine-mesen-

cephalic reticular formation. This two-way system has thalamic (dorsomedial nucleus), extrapyramidal and cerebellar subcircuits. Interruption of this first circuit produces release of the segmental micturition reflex from volitional control, a low threshold detrusor reflex, and small bladder capacity (uninhibited neurogenic bladder). Enlarging ventricles may disrupt subcortical frontal lobe connections, subcortical and medial frontal lobe lesions being most often associated with release of detrusor reflex.¹³ The same anatomical argument concerning the effect of enlarging ventricles on the lower extremity motor fibers can be applied to medially originating suprasegmental bladder fibers. This complex first circuit is considered intact if the patient is able to suppress the detrusor reflex on command.

Patients with parkinsonism have dopamine neurotransmitter deficiency in the striatum and substantia nigra, and often have neurogenic bladders. Following ventro-lateral thalamotomy in patients with parkinsonism, an uninhibited neurogenic bladder may either disappear, if previously present, or appear for the first time. The similarity between the clinical picture of NPH and parkinsonism, and the presence of uninhibited neurogenic bladder in both has led to speculation as to a common site of neuronal dysfunction.¹⁵

The second neuronal circuit provides the final common pathway of suprasegmental bladder influences, and connects the brain stem reticular formation to detrusor motor neurons located in the intermediolateral sacral spinal cord grey matter. A third loop is composed of detrusor and pudendal neurons and interneurons in the sacral grey matter. A fourth, single neuron circuit connects pyramidal cells in the motor cortex, and pudendal motor neurons in the sacral cord. Involvement of the fourth circuit is tested clinically by ability to voluntarily contract the urinary sphincter. A fusimotor or gamma efferent subsystem is also operative at the level of the pudendal nerves.

Neuropharmacological drugs which affect the parasympathetic nervous system alter bladder function. Cholinergic drugs enhance weak bladder contractions, and anticholinergics depress overactive detrusor function.

Ventricular dilatation, any increased transmural pressure gradient, periventricular interstitial edema or any other unknown pathophysiological mechanism of NPH would seem to be operative only on the first and fourth circuits because of the anatomic proximity of these circuits to the expanded ventricles. Theoretically, both these circuits might be involved and contribute to the production of incontinence. That the enlargement of the ventricles is of fundamental importance in the production of the clinical signs in NPH would seem to follow logically from the observation that an identical syndrome is often present in internal obstructive hydrocephalus, such as occurs in aque-

ductal stenosis.¹⁹ Any theory concerning the mechanism of NPH would have to explain the phenomenon that the neuronal circuit dysfunction is sometimes rapidly reversible following shunting.

An uninhibited neurogenic bladder is the expected cystometrographic finding in a patient with NPH. The pressure-volume curve would predictably shift to the right following shunt surgery, and bladder function and capacity improve. Prior to the development of frank incontinence, urinary frequency, nocturia, and urgency might herald the onset of uninhibited neurogenic bladder dysfunction. If the overtly incontinent patient is questioned closely, a history of urge incontinence may be elicited. A characteristic cystometrogram even without clinical incontinence would be helpful in defining impaired neuronal dysfunction in subcortical frontal lobe circuits. Unfortunately, an uninhibited neurogenic bladder is also commonly found in patients with cerebral vascular, atrophic, and degenerative diseases which form the differential diagnosis of NPH.¹⁷ A suggestive cystometrogram would not help in this differential diagnosis, but would be useful in excluding other causes of urinary incontinence. A negative cystometrogram, or one with a pattern other than the uninhibited neurogenic type would suggest that shunting might not improve the patient's urinary symptoms.

CONCLUSIONS

No satisfactory definition of normal pressure hydrocephalus exists, and as a corollary, no accurate predictor of patients that improve with shunting has been found.

Urinary incontinence is only the end point of a symptomatic uninhibited neurogenic bladder secondary to involvement of subcortical frontal lobe circuits. Frequency, nocturia, and urgency simulating bladder outlet obstruction or urinary tract infection are symptoms of lesser involvement of the same circuitry.

Careful and complete cystometrographic examination should be carried out as an extension of the clinical evaluation, and provides meaningful information in the evaluation of patients with suspected NPH.

A trial of medical treatment with anticholinergic agents should be considered in a symptomatic NPH patient, after shunting, if urinary frequency, urgency, and incontinence continue. If the patient is not considered a shunt candidate, and is symptomatic, such treatment might also be helpful.

The selection of the demented patient for a shunting procedure should not be based on any one laboratory test. The clinical features, associated diseases, the patient's physiological age, socio-economic factors, and the patient's and family's attitude are all important variables in the shunt decision formula.

The patients with a specific underlying etiology

have a favorable prognosis.

Computerized tomography will be increasingly employed as a screening test in the evaluation of dementia, and should significantly reduce the number of patients subjected to invasive procedures.

SUMMARY

A patient with NPH and urinary incontinence is presented. The urinary incontinence cleared dramatically following ventriculoatrial shunting. Preoperative and postoperative cystometrographic findings, employing the CO₂ insufflation technique, are presented. The concept of NPH is discussed and the unsatisfactory status of the definition of the disorder is emphasized. The clinical findings are considered non-specific etiologically, but typical of frontal lobe dysfunction. Some current disconnection hypotheses of frontal lobe dysfunction are mentioned. The various tests and diagnostic procedures are reviewed in chronological sequence. The limitations of predictive value are noted. Relevant neuroanatomy and the probable location of the neuronal circuit disturbance causing incontinence are discussed. Some conclusions about NPH, selection of patients for shunting, the value of cystometry, and non-surgical treatment of urinary symptoms are made.

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Polyposis, Gliomas, and Multisystem Disease

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ABSTRACT

A family history is presented as an example of Turcot's syndrome and new findings are described. We suggest that familial polyposis, Gardner's, Turcot's and Wermer's syndromes, are probably related through a common cellular origin but that the clinical presentation may be different due to variability of gene penetrance.

In 1949, Crail¹ described a patient with rectal polyposis, medulloblastoma and thyroid carcinoma. Ten years later Turcot² reported familial polyposis in a brother and sister who both had central nervous system tumors. The brother died of a medulloblastoma of the spinal cord and the sister died of a glioblastoma. An autopsy of the girl disclosed that she also had a chromophobe adenoma of the hypophysis.

Yaffe,³ in 1964, reported a woman with epidermal cysts, fibromas and gastric polyps whose uncle had a glioblastoma and multiple polyps of the colon.

In 1969, Baughman⁴ described a second family with Turcot's syndrome. Some of his cases had pigmented nevi and others cafe-au-lait skin changes.

We report here a family with gliomas, polyposis coli, and lichen ruber moniliformis (Figure 1).

CASE REPORTS

Case #1 — A 30-year-old female presented with seizures in April 1972. At craniotomy, a glioblastoma multiforme of the right parietal temporal region was removed. This was followed by a course of radiation therapy and the patient made a good recovery. In June 1973, a routine sigmoidoscopy revealed one three-millimeter adenomatous polyp at eight centimeters. It was also noted that the patient had lichen ruber moniliformis. No other abnormalities have been noted.

Case #2 — A 34-year-old female underwent colectomy for familial polyposis in 1971. Malignant changes were found at the time of surgery. Several years ago she was reported to have Darier's disease but this has been renamed lichen ruber moniliformis. Otherwise she remains well.

Case #3 — A male died at the age of 15 in 1958 of an astrocytoma of the brain. No other information is available.

Case #4 — This six-year-old child has skin changes identical with his mother (Case #2) and aunt (Case #1) which appear to be typical of lichen ruber moniliformis. The child's gastrointestinal tract has not yet been investigated but he is asymptomatic.

Case #5 — This 53-year-old female has lichen ruber moniliformis. Barium studies do not reveal polyposis and she remains well.

Case #6 — This is a 74-year-old female in good health but reportedly has skin changes described as "bleeding warts" on the back.

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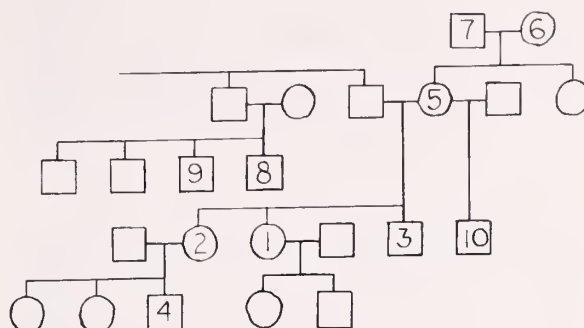


FIGURE 1

Case #7 — A 64-year-old male in 1965 died after total colectomy for ulcerative colitis.

Case #8 — This 34-year-old male was treated with radiation therapy for a pituitary adenoma in 1970. He had been doing well until recently when he experienced some seizure activity. The diagnosis of a glioma has not yet been excluded.

Case #9 — A 38-year-old male has undergone a left simple mastectomy in 1970 for malignant melanoma.

Case #10 — A 20-year-old male has refused a gastrointestinal work up but is in apparent good health.

DISCUSSION

Familial gliomas are uncommon representing less than 1% of all brain tumors. The link in this family with polyposis coli appears to be an example of Turcot's syndrome. The association with lichen ruber moniliformis may be a variant of this syndrome. The skin changes are a new finding and appear to be the common thread running through this family. They may also provide a useful marker in screening the six-year-old child (Case #4) for subsequent malignant disease.

The link with the maternal grandparents of the index case seems remote although the history of "bleeding warts" suggests some underlying skin abnormality in Case #6. The malignant melanoma (Case #9) may also be related since pigmented nevi have been noted as part of the disease complex. Turcot² reported a chromophobe adenoma in his original family and it is seen again in a cousin here (Case #8).

Familial polyposis has now been described in association with a wide variety of abnormalities including osteomas, fibromas and sebaceous cysts, as in Gardner's syndrome. However, these variants are relatively rare. In Bussey's⁵ series of 127 polyposis patients, only one-third of the total cases had lesions that even remotely resembled Gardner's syndrome.

In searching for a unifying concept one wonders

whether some of these conditions represent different expressions of the same disease complex. According to Weichert,⁶ endocrine glands which secrete peptide hormones all develop from neural ectodermal cells which migrate into the alimentary tract. He suggests that multiple adenomas of the endocrine glands (Wermer's syndrome), including chromophobe adenomas, have the same embryonic origin. Weichert⁶ indicated that carcinoids, which secrete melanocyte stimulating hormones, and thyroid carcinoma may be related in the same way. Both abnormalities are found in variants of Gardner's syndrome. It is tempting to extend this thesis to cases reported above.

Familial polyposis may be either dominant or recessive. Veale⁷ noted that those patients with dominant disease usually present earlier in life with up to 1000 polyps, whereas the recessive form usually have only a few polyps, always less than 150, which develop later in life. He also hypothesized that there may be two different genes controlling adenoma formation or possibly varying gene penetrance, giving rise to different clinical pictures. This variability may be expressed in these three different syndromes.

It seems likely that all of these cases belong to a wide spectrum of diseases involving the colon, brain, skin, and other organs. Many of these abnormalities are potentially malignant and conse-

quently their early recognition is important. The familial defect suggests that there may be a genetic tendency towards de-repression on adjacent alleles which may sometimes predispose to malignancy.

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The MB Isoenzyme of Creatine Kinase in the Diagnosis of Myocardial Infarction

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Over the past several years, numerous enzyme determinations have been utilized in an attempt to diagnose myocardial infarction. Serum glutamate-oxalacetic transaminase (SGOT), lactic dehydrogenase (LDH), hydroxybutyrate dehydrogenase (HBD), creatine kinase (CK) and/or combinations thereof have been suggested as ideal methods in establishing early myocardial damage. However, a major concern has been the general lack of specificity of these tests. More recently, isoenzyme determinations were purported to increase specificity in detecting tissue destruction. Presently, it is generally accepted that determination of the MB isoenzyme fraction of Creatine Kinase (MB-CK) represents the most specific and sensitive method of detecting myocardial ischemia.^{1,2} Although elevated total CK values may be seen in a variety of conditions (e.g., pulmonary thromboembolism, cerebral vascular accident, muscle injection, pancreatitis, hypothyroidism, convulsive disorders and electro cardioconversion), the MB isoenzyme is rarely elevated except in cases of myocardial infarction. Values of MB-CK will become elevated approximately 6 hours after the initial ischemic episode with subsequent disappearance within 24-36 hours. Thus, it can provide the physician with early supportive evidence that infarction has occurred. Various investigators have reported a 10-34% incidence of recent infarction in which the electrocardiographic changes consisted of only non-specific S-T segment or T wave abnormalities.³ Elevated MB-CK values therefore assume even greater diagnostic import where specific electrocardiographic evidence of infarction is lacking.

Galen⁴ has suggested that a MB-CK value of greater than 3% of the total CK is considered diagnostic for myocardial infarction particularly when it is combined with a "flipped" LDH (LDH₁>LDH₂). Blomberg, et al⁵ reported similar findings for MB-CK but did not suggest the routine use of LDH isoenzymes on the basis that they were of little use in early diagnosis and lacked the specificity of the MB-CK isoenzyme. In the past, we have utilized both CK and HBD in evaluating our cardiac patients. With institution of a newer column chromatographic fractionation technique in assaying MB-CK isoenzymes, we have been impressed with the singular importance of this

determination in assessing early myocardial damage. It is the purpose of this paper to review our present methodology of MB-CK isoenzyme determination and to assess the efficacy of this test in the diagnosis of myocardial infarction.

SUBJECTS, MATERIALS AND METHODS

A total of 174 patients admitted to Mercy Hospital from October 1975 to April 1976 were studied. Each of these had at least one Cardiac Enzyme Profile performed which consisted of a total CK and HBD drawn upon admission followed by one additional set of enzymes on the day 2 and day 3 of hospitalization. The samples were immediately centrifuged, the serum removed and stored at 4 C until assayed. Creatine Kinase (CK) and α -hydroxybutyrate dehydrogenase (HBD) activity were determined on each specimen at 30 C using a Gilford 3400 system (Oberlin, Ohio 44074). CK activity was determined according to a modification of the Oliver⁶ and Rosalki⁷ methods using Worthington's CPK n-1 substrate (Freehold, N.J. 07728). Normal values: Men = 0-80 IU/L, Women = 0-50 IU/L. During this time, at least one MB-CK isoenzyme value was determined where the total CK value was elevated or showed a definite rising or falling trend.

CK isoenzymes were fractionated according to the column chromatographic method of Nealon and Henderson^{8,9} with the following modification: all buffers contained 1 mM dithiothreitol (DTT). The MM-CK and MB-CK fractions were manually assayed at 30 C on the Gilford 3400.

The protocol for measuring each fraction was the same with the exception that a fivefold dilution of the MM-CK fraction, made with its respective elution buffer, was used. One ml of sample was mixed with 1 ml of concentrated CPK n-1 substrate (reconstituted with one-half the normal amount of distilled water) and allowed to incubate at room temperature for four minutes. The mixture was then aspirated into the thermocuvette, allowed to incubate 30 seconds and then the change in absorbance recorded over the next four minutes. A substrate blank consisting of 1 ml of MB-CK elution buffer and 1 ml substrate was run with each determination to insure that the absorbance change was no greater than .002 units. Isoenzyme activity in IU/L was calculated by multiplying the absorbance change over four minutes by an appropriate factor.

The upper limits of normal for MB-CK (as determined from a previous study in our laboratory)

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TABLE 1

COMPARISON OF FINAL DIAGNOSIS TO CK AND MB-CK VALUES				
Group	Number	M.I.	Elevated Total CK	Elevated MB-CK*
I-A	39	NO	NO	—
I-B	15	NO	YES	NO
I-C	1	NO	YES	YES
II-A	49	YES	YES	YES
II-B	2	YES	YES	NO
II-C	1	YES	NO	NO

*MB-CK was considered abnormal if the % MB and/or the quantitative amount (IU/L) were above critical values.

were designated as <3% of total CK and quantitatively <4 IU/L. Values above these levels were considered indicative of myocardial necrosis.

To more accurately assess the "true diagnostic" value of our MB-CK isoenzyme technique as it related to myocardial infarction, the following statistical parameters were also determined:

Sensitivity = positivity in disease expressed as %

Specificity = negativity in health or absence of a particular disease expressed as %

Efficiency of test = % of patients correctly classified as diseased and non-diseased.

RESULTS

Of 174 patients reviewed, 67 had no clinical, electrocardiographic or enzyme evidence to justify a diagnosis of recent infarct. One hundred and seven (107) patients had either clinical symptoms and/or electrocardiographic findings suggesting possible myocardial infarction. Of these 107 cases, two major groups emerged: Group I — Fifty-five (55) patients who were subsequently identified as having no recent evidence of infarct and Group II — Fifty-two (52) patients who were discharged with a final diagnosis of myocardial infarction. Table 1 summarizes the data for these two groups.

Of the 55 cases in Group I, the MB-CK levels were determined in 16 cases in which the total CK values were elevated. The remaining cases showed no elevation of total CK nor a progressive trend in subsequent determinations. In fifteen of these cases (Group I-B), the correlation between the negative isoenzyme results and the final diagnosis was excellent. However, in Group I-C, there was a single case in which ultimately clinical and ECG evidence failed to support the positive isoenzyme results. This patient (Total CK = 601 IU/L, MB-CK = 4.6 IU/L) suffered fracture of four ribs and extensive contusion of the chest wall. This case must be considered a false positive.

Out of the 52 cases in Group II, there were 49 (II-A) in which the abnormal isoenzyme results agreed with the final diagnosis. In Group II-B, there were two patients in which the total CK was elevated but no abnormality in MB-CK was noted. Of these, one patient discharged himself against

TABLE 2

THE SENSITIVITY, SPECIFICITY AND EFFICIENCY OF CK AND MB-CK IN DIAGNOSIS OF MI		
	CK	CK-MB
Specificity	71%	94%
Sensitivity	98%	94%
Efficiency	84%	94%

medical advice making further study impossible. The remaining patient had a definite infarct of at least 3 days' duration prior to obtaining the first specimen in which case it may have been too late to detect elevated MB-CK activity. In Group II-C, neither the total CK or the MB-CK was elevated. In this case, the infarct was estimated by history to have occurred 7 days prior to admission.

Table 2 illustrates the sensitivity, specificity and efficiency of total CK verses MB-CK in relation to the final diagnosis.

Obviously, if one could exclude the cases from Group II-B and II-C (Table 1) where appropriate blood samples were unable to be obtained, these 3 parameters approach 100% for MB-CK.

It should be noted that HBD determinations were also performed on the above 107 cases but in no instance did they contribute significant diagnostic information over that gained by the combination of total CK and MB-CK.

DISCUSSION

The results of this study support the findings of previous investigators indicating that the MB-CK isoenzyme is currently the most reliable test available for correctly diagnosing myocardial infarction.^{1,2,5} Specificity of the MB-CK isoenzyme determination in this study was 94% as compared to 71% where only total CK values were employed. The sensitivity of the MB-CK fraction in assessing infarction was also 94%. Had it not been for two patients in the series in whom blood specimens were obtained several days post-infarction, the sensitivity of the test would approach 100%. Sensitivity was enhanced by determining both relative MB-CK % as well as specifically quantitating the MB-CK fraction. In six cases from Group II, only one of these two parameters was elevated. Thus, by measuring both determinants, greater interpretive value was obtained from the isoenzyme assay.

It should be emphasized that the principle reason for selecting the column chromatography fractionation technique over an electrophoretic method was because the former allows for the direct measurement of MB-CK activity in the critical range of 1-10 IU/L. In this range, the precision of the method showed a coefficient of variation of <4%. Increased sensitivity in quantitating the MB-CK fraction also provides important interpretive information in those patients in whom myocardial necrosis becomes superimposed upon other

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The Diethylstilbestrol (DES) Exposed Female in Maine

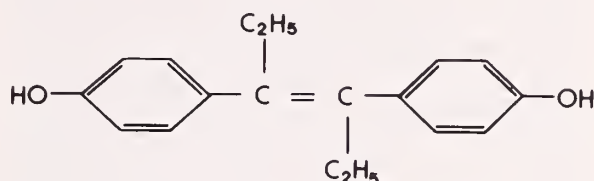
A Discussion With Suggestions Regarding Identification and Management Applicable to Our State

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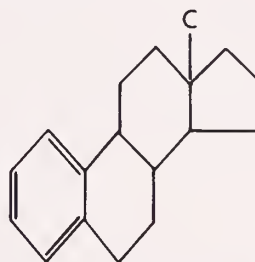
In the middle 1940's, a report by O. Watkins Smith¹⁹ described the results of a five-year study using Diethylstilbestrol (DES)* in the prevention and treatment of complications of pregnancy, such as previous abortion, miscarriage, premature labor, or bleeding during pregnancy. The overall improvement in the outcome of pregnancy suggested by the study led to the widespread use of DES, Diestrol,[®] Hexestrol or a combination of these non-steroidal estrogens (Figure 1) in the United States during the late 1940's and 1950's.^{5,23,17} By the late 1950's, the use of this regimen had decreased markedly. Further studies had by this time showed there was indeed no improvement in pregnancy salvage rate. Then in the mid-1960's, the first cases of clear cell adenocarcinoma of the vagina and cervix in young women began to appear. It is to be remembered that carcinoma of the vagina is uncommon, accounting for only one to two percent of all female genital malignancies,¹⁴ and is a disease of older females — those in the 50-70 year age group.⁶ In addition, vaginal carcinoma is predominantly squamous and only rarely is it adenocarcinoma. Indeed until 1967, only six documented cases had been reported in the world's literature¹⁸ and only three were in young females, i.e., less than 30 years old.²³

Herbst and Scully were the first to report vaginal adenocarcinoma appearing in young women under the age of 25.⁷ These cases were studied in detail and it was found that in seven of eight the mothers of these patients either bled during pregnancy, threatened to abort or had been considered as chronic aborters, and therefore, had received DES.⁸ From Herbst's analysis, the suggestion was made of the association between vaginal adenocarcinoma and maternal DES therapy.

The timing, dosage, and duration of maternal non-steroidal estrogenic therapy associated with cases of adenocarcinoma of the vagina in female offspring have varied widely. In all cases in which information could be obtained, the drug therapy



Diethylstilbestrol (DES)



Representation of the Estrogen parent nuclei "Estrane," a C-18 steroid.

Fig. 1

Credit line: Maine Medical Center, Medical Photography Dept., 22 Bramhall Street, Portland, Maine 04102.

was started prior to the fifth month of gestation. Dosage as low as 1.5 milligrams of DES throughout pregnancy as well as duration of exposure as short as 7 days in the first trimester has been recorded in association with the delayed development of carcinoma.^{5,10} Today, approximately 280 cases of adenocarcinoma of the vagina and cervix have been described, all within the ages of 10-30 years.

But while this adenocarcinoma has captured public attention, there remains a large reservoir of females in whom no gross carcinoma has been observed, but in whom there is a positive or suspicious maternal history of DES usage during early gestation. Several gross physical abnormalities have been observed: 1) cock's comb cervix, 2) para-cervical collar, 3) transverse vaginal ridge, 4) vaginal hood, and 5) the granular, or "strawberry" cervix. Studies seem to indicate approximately 40

*"DES" will be used throughout the article to symbolize all non-steroidal estrogens.

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percent^{2,11} of all females having been exposed to DES in the early part of gestation would show a grossly visible abnormality of one sort or another, as mentioned. However, more recent studies by Antonelli,¹ Schmidt, and Stafl,²⁰ using colposcopy, have shown the incidence of vaginal abnormalities approaching 90 percent.

The remaining portion of the discussion revolves around those patients having been exposed to DES but who appear at present to show no evidence of either adenocarcinoma of the vagina or the benign gross lesions just described. The most common finding noted to date in these females is vaginal adenosis, a term used to described areas of the vagina covered by columnar epithelium where normally squamous epithelium is expected.

It is worthwhile to briefly review the embryology of the vagina in an attempt to explain the pathogenesis of this disorder. Apparently the vagina is formed by its mullerian anlage (of columnar epithelium) being undermined by the vaginal plate, a solid core of squamous epithelium, probably originating at the urogenital sinus, which then extends in a cephalad direction. This vaginal plate ultimately becomes canalized to form the permanent lumen lining of the vagina.¹³ The process starts at about the eighth week of gestation and is completed by the 18th or 20th week. Since the original vaginal epithelium is of mullerian origin and columnar,^{9,18} it is reasonable to speculate that adenosis results when the anlage is not completely replaced by the upgrowing place of squamous epithelium due to inhibition by a teratogenic factor, possibly DES. Indeed, this has been seen experimentally in the offspring of animals exposed to DES in early gestation and may well be the basis of an explanation of vaginal adenosis. Once established, vaginal adenosis remains.

But what is its significance? Let us begin by saying that no one knows the exact prognosis of adenosis in these young females. Some reports seem to indicate the possibility of this vaginal columnar epithelium (while undergoing squamous metaplasia i.e., squamous epithelium replacing the columnar), developing squamous abnormalities — progressive dysplasia or even carcinoma in situ.^{21,4} However, other investigators have not yet found this to be so.¹ It is felt by some that adenosis of the vagina should be considered abnormal in itself and removed completely or at least extensively biopsied.¹⁷ However, as you can readily understand, the excision of a large area of the vagina might well lead to sexual crippling, sexual incapacity, or sterility due to infection, hemorrhage, scarring, and foreshortening of the vagina. Herbst²² has suggested the use of progestational suppositories, hoping to stimulate squamous metaplasia; however, no controls are available. In addition, perhaps it is dangerous to conceal abnormal columnar epithelium.

However, the points all investigators agree upon are the identification and thorough pelvic examina-

tion of the DES-exposed female. A Pap smear obtained blindly cannot be accepted as an effective screening test.² Therefore, as an aid to physicians, the following points are emphasized:

1. Patients between the ages of 10 and 30 must be questioned regarding the possibility of DES exposure in utero. Significant maternal history indicating potential use of non-steroidal estrogens during the years 1945-1960 included:
 - a. previous abortion or miscarriage.
 - b. spotting or uterine bleeding during pregnancy (threatened abortion).
 - c. previous history of premature labor.
 - d. history of known essential hypertension.
 - e. diabetes mellitus.

If the history is suggestive or positive, the next step is dependent upon the age of the patient and the presence of any symptoms.

2. Premenarchal females without symptoms need not be examined pelvically. IDENTIFICATION of these young people and informing the parents of the significance of DES exposure becomes a primary objective.
3. However, in premenarchal females with any symptoms, i.e., vaginal spotting or bleeding, pain or development of a pelvic mass, examination is mandatory, even under anesthesia if need be. Procrastination in the face of any of these is to be condemned. It must be remembered that genital carcinoma in young females usually causes vaginal bleeding or spotting and in many cases this has been mistaken for the dysfunctional bleeding of adolescence. This assumption has often delayed the correct diagnosis. Therefore, history of abnormal vaginal bleeding or staining in patients of this age group can no longer be assumed to be due to anovulation.^{15,16} It is of interest to note that in Herbst's initial study⁷ of seven patients ranging in ages from 15 to 22, all were shown to have had a history of abnormal vaginal bleeding up to eighteen months prior to diagnosis. Five of the seven were then treated with various hormonal medications but without benefit of pelvic exam, and even with no response to medication there was still delay in pelvic examination and ultimate diagnosis.
4. For the postmenarchal individual (or the premenarchal symptomatic female) thorough pelvic examination is advocated including direct visualization of the entire vagina and cervix, directed Pap smears, palpation of the anterior and posterior vaginal walls (most commonly where carcinoma is found), along with iodine staining of the vaginal and cervical epithelium. Representative biopsies are then taken of all abnormal areas noted. Patients are to be then followed with repeat exams every six months to a year.
5. Colposcopic examination, now being performed by an increasing number of gynecologists,

cologists in Maine, is to be strongly encouraged. With the use of the colposcope, accurate delineation and description of vaginal and cervical abnormalities, followed by directed biopsies, can be made.

6. Finally, as Richart²² has emphatically stated, the examining physician should not perform any therapy, i.e., excisional biopsy, cauterization or cryocauterization until the abnormal Pap smear or biopsy has been reviewed. The histology and pathology of the vagina and cervix in the DES exposed female is most complex; and requires an expertise of interpretation that to date is held by few. A national registry is being established to review all cervical and vaginal noninvasive lesions found in these DES-exposed females. Physicians will be encouraged to consider submitting any abnormal tissue for further study by this group.

What, then, does this signify to Maine? First, we must look at numerical studies. The population of Maine during the 1950's and 1960's was nearly one million, representing 0.75 percent of the total population of the United States at that time. The estimation of the female population in the United States exposed to DES in utero ranges between 500,000 and 2,500,000 individuals. Hence, we are faced with the fact that between 4,000 and 15,000 females exposed to DES are in our State today. To date, two cases of adenocarcinoma of the vagina have been discovered in Maine; another 150-200 females have been examined colposcopically. Hence, it is obvious that further work needs to be done.

The Maine Division of the American Cancer Society has agreed to support efforts to identify these at-risk females in Maine. Physicians throughout the State will be asked to support the concept of a central DES registry. This registry, located in Brunswick at the American Cancer Society headquarters, will be available for all physicians. The registry will collect statistics, providing assistance and information for physicians as well as patients. It is tentatively planned that gynecologists (and interested physicians), strategically located throughout the State and knowledgeable about DES, will be available for consultation at the local level.

Hopefully, we in Maine will be able to contribute to the understanding of this most serious

problem and to offer reassurance to these young DES-exposed females.

Plans are being made to mail with the August issue of "CA-A Cancer Journal for Clinicians" copies of the projected registry forms. Questions dealing with timing, amount of drug exposure, and physical findings are to be included. Patient and parent information sheets are also being developed.

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Pharmacotherapy of Cardiopulmonary Arrest

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Effective cardiopulmonary resuscitation (CPR) requires well-coordinated control of ventilation, assistance of circulation, and definitive treatment of abnormalities in cardiac rhythm and function. A systematic approach can decrease mortality, but the overall survival following cardiopulmonary arrest in the general hospital setting is no more than 20% (Lemere and Johnson, 1972). Nevertheless, potentially reversible sudden cardiac arrest is common following acute myocardial infarction. Furthermore, accidental death from cardiac arrest can occur in young, otherwise healthy individuals due to drug overdosage, electrocution, motor vehicle accidents, and drowning. Although a critical cost-effectiveness analysis of CPR might not prove to be favorable, the potential for lifesaving intervention in even a small number of cases justifies continued efforts in perfecting the technology of CPR.

Much literature is available on the basic techniques of CPR. This article will focus on definitive measures and on pharmacologic aspects of resuscitation. Since CPR is clearly not conducive to controlled clinical trial, most of our recommendations of pharmacotherapy are based upon clinical experience rather than sound data.

ORGANIZATION OF THE TEAM

To the casual witness, CPR is a chaotic event. Orders are shouted, syringes fill the air, medication vials pop and fragment, the victim is pumped and ventilated, and miles of EKG paper accumulate underfoot. In general, however, the appearance belies disorganization. Most medical centers have a specific "cardiac arrest" team that rapidly as-

sembles in any part of the hospital when summoned. The team usually includes three or more physicians, one or more nurses who are skilled in cardiovascular therapy, and sometimes a respiratory therapist and clinical pharmacist. The senior physician directs the resuscitation effort. Another physician — ideally an anesthesiologist adept at endotracheal intubation — attends to respiratory care, while a third physician applies closed-chest cardiac massage. Nursing and pharmacy staff, working from a mobile resuscitation or "crash" cart, prepare the necessary drugs for administration and record them on a flow sheet.

INITIAL MEASURES

Assessment

The patient requiring CPR usually is apneic, cyanotic, unresponsive, and has absent peripheral arterial pulses. CPR must be initiated immediately or the patient will die. Untreated cardiac arrest usually leads to irreversible central nervous system damage within ten minutes. Persons who first encounter the victim should initiate CPR as described below and summon the resuscitation team.

Initial Treatment

Initial therapeutic measures are designed to provide "stop-gap" support of vital life functions until more definitive resuscitative measures are begun and while they are proceeding. The order in which we describe specific measures does not imply that they should be done in that order. Ideally, members of the team are performing these techniques simultaneously.

Precordial blow. When cardiac arrest is witnessed, a brisk blow to the precordium with a closed fist may be all that is needed to restore normal cardiac action. How often this is successful is not established. However, the precordial blow carries little or no risk, wastes essentially no time, and should be tried on all patients.

Assisted ventilation. A cuffed endotracheal or nasotracheal tube is inserted, the bronchial tree is suctioned, and assisted "bag" ventilation begun with 100% oxygen. Since intubation can prove difficult or impossible for inexperienced personnel, it is essential that an individual adept at this proce-

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dures be part of the resuscitation team.

Cardiac massage. Closed-chest cardiac massage using appropriate technique is begun in coordination with assisted ventilation.

Direct-current cardioversion. "Blind" cardioversion or defibrillation is generally recommended even before cardiac rhythm is determined. An energy output of 400 joules (watts x seconds) is usually employed, and it may convert ventricular tachycardia or fibrillation to an organized rhythm without producing damage to the myocardium. Defibrillation is not recommended in children and should be deferred for several minutes in cases of cardiac arrest from hypoxia.

Establishment of an intravenous route. Reliable access to the systemic circulation is essential to resuscitation efforts. Indwelling plastic catheters are clearly preferable to butterfly "scalp-vein" needles which often dislodge during resuscitation. The catheter is inserted into a large peripheral vein and taped securely in place. If possible, the cannula should reach the "central" venous circulation. Drugs are more likely to be effective when injected centrally, particularly if peripheral circulation is poor. Furthermore, many cardiovascular drugs used in CPR are highly irritating to smaller peripheral veins.

Unfortunately, antecubital and forearm veins often are difficult to cannulate. Therefore, a physician adept at cannulation of the right subclavian vein or at performing "cutdowns" at antecubital or medial malleolar sites should be available to the team.

Cardiac monitoring. Continuous electrocardiographic (ECG) monitoring is begun using a conventional ECG or an oscilloscopic monitor. Knowledge of the electrophysiologic mechanisms of the arrest is essential to the choice of appropriate pharmacotherapy.

Follow-up Assessment and Treatment

Completion of these supportive measures usually ensures that more definitive resuscitation efforts can begin. However, the adequacy of cardiovascular support must be assessed frequently, and adjustments made as necessary. Of particular importance is the reversal of acidosis and hypoxia.

Correction of acidosis. Bicarbonate therapy is begun as soon as an intravenous route is established. Sodium bicarbonate can be given as a continuous infusion of 5% solution, or by repeated bolus injections from commercially available prefilled 50-ml syringes, each containing 45 to 50 mEq of sodium bicarbonate. Many physicians prefer the bolus approach since it is easier to titrate. In an adult, one or two ampules are administered initially; the initial dose is followed by one ampule every five to ten minutes as resuscitation proceeds. Repeated measurements of arterial blood pH and carbon dioxide tension ($p\text{CO}_2$) are necessary for appropriate titration.

Correction of hypoxia. Adequacy of ventilation is assessed by repeated measurement of arterial blood gases, including oxygen tension ($p\text{O}_2$), as well as pH and $p\text{CO}_2$. Overzealous bicarbonate therapy and/or ventilation can lead to metabolic and/or respiratory alkalosis, which can impair definitive resuscitation.

Adequacy of circulation. Closed-chest massage is generally adequate if femoral and carotid pulses can be felt. A decrease in pupil size suggests that the brain is receiving an adequate supply of oxygenated blood.

Aspiration of gastric contents. Restoration of cardiovascular function may be difficult or impossible if the patient has aspirated acidic gastric contents. Material seen in the pharynx at the time of intubation or liquid suctioned from the bronchial tree may be tested with commercially available pH paper strips. A low pH (3.0 or less) suggests that acid aspiration has occurred. Although a definitive method of treating this syndrome is not established, it is usually recommended that a pharmacologic dose of corticosteroid (i.e., 200 mg of hydrocortisone) be injected intravenously as soon as possible.

CARDIOVASCULAR PHARMACOTHERAPY

Definitive therapy to restore cardiac action can begin early in the course of CPR, but it is not likely to succeed unless circulation is adequately supported, acidosis reversed, and hypoxia corrected. The approach to pharmacotherapy depends upon the electrical mechanism of the arrest. *Stimulatory* treatment is undertaken when bradycardia, asystole, or "flat-line" is observed on the ECG. *Suppressive* treatment is indicated when the monitor reveals ventricular tachycardia, ventricular fibrillation, or another tachyarrhythmia which is incompatible with life. The ECG must be continuously monitored as therapy proceeds. Not uncommonly the electrical findings will abruptly shift from asystole to tachyarrhythmia or the reverse, necessitating a sudden change in pharmacotherapy.

Suppressive Therapy

When the pattern of ventricular contraction is chaotic or excessively rapid, cardiac output becomes insufficient to maintain life and suppressive therapy is indicated. Ventricular tachycardia and fibrillation are the most common of such arrhythmias (Figures 1 and 2). Occasionally, supraventricular tachyarrhythmias can be very difficult to distinguish from ventricular tachycardia. Although supraventricular tachyarrhythmias may respond to relatively benign measures such as carotid sinus massage or intravenous edrophonium, ventricular tachycardia will not. Accordingly, one is obliged to approach any life-threatening ventricular tachyarrhythmia by using the measures described below, even if a supraventricular origin has not been ruled out.

Direct-current cardioversion. Defibrillation is

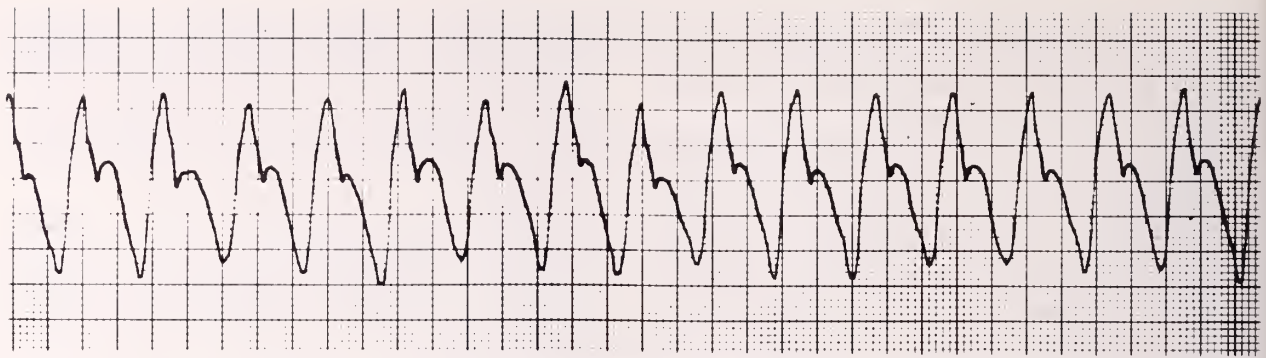


Fig. 1. Monitor tracing of ventricular tachycardia in a patient with acute myocardial infarction.

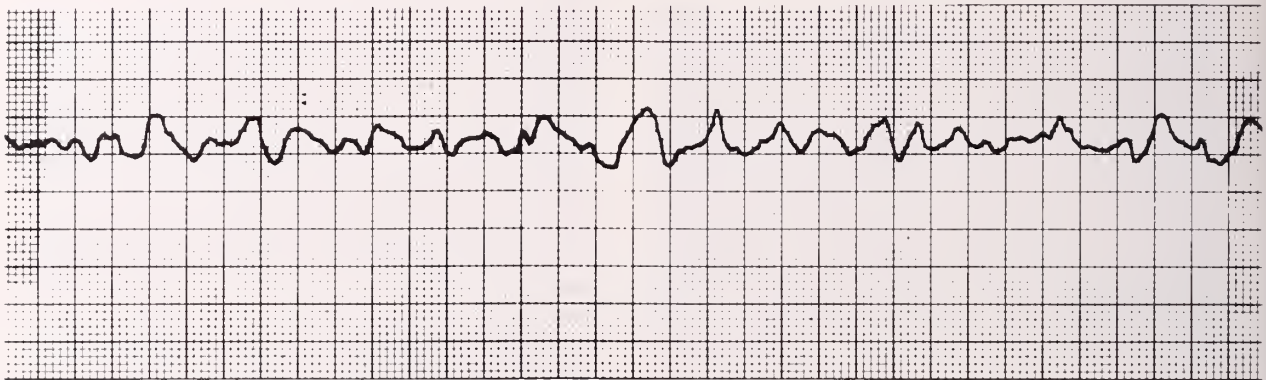


Fig. 2. Monitor tracing of ventricular fibrillation in a patient with acute myocardial infarction.

the definitive maneuver, using an energy output of 200 to 400 joules. If a pattern of "fine" ventricular fibrillation appears on the ECG, epinephrine (0.5 mg) is given intravenously to convert the fibrillation pattern to a "coarse" one prior to the shock. Direct current cardioversion is repeated as often as necessary and combined with antiarrhythmic drug therapy if indicated.

Antiarrhythmic drugs. Several drugs are available in the United States for the treatment of ventricular tachyarrhythmias. In CPR they are usually administered in succession until the arrhythmia is suppressed.

1. *Lidocaine* is considered the drug of first choice. A bolus loading dose of approximately 100 mg is given intravenously, and an infusion of 2 to 4 mg per minute started simultaneously. A second 50 to 100 mg bolus is usually needed 10 to 30 minutes after the first one in order to maintain effective plasma concentration in the period before the infusion has produced sufficient accumulation. It is usually taught that therapeutic doses of lidocaine have little or no effect upon cardiac contractility or conduction. However, in susceptible individuals lidocaine does have the potential to produce heart block, hypotension, and cardiovascular collapse. Grand mal seizures can occur following high doses of lidocaine.
2. *Procainamide* is infused intravenously at 25 to 50 mg per minute to a maximum dose of 1.0 gm.

Although an effective antiarrhythmic, procainamide produces dose-dependent cardiac depression and may cause or potentiate hypotension if infused too rapidly.

3. *Phenytoin (diphenylhydantoin, DPH)* is less effective than lidocaine or procainamide. Many physicians would bypass DPH and use propranolol instead. DPH is given intravenously at 50 mg per minute to a total dose of 500 mg. Rapid infusions can cause bradycardia, heart block, and hypotension, possibly due to the very irritating propylene glycol-containing alkaline solvent. Since DPH is poorly water-soluble at physiologic pH, it should be infused directly into a vein rather than into another intravenous tubing system in which precipitation may occur.
4. *Propranolol* can be given intravenously at 1 to 2 mg per minute, to a total dose of 5.0 mg. Contrary to popular mythology, propranolol produces essentially no direct cardiac depression at concentrations in the therapeutic range. Propranolol may indirectly impair cardiac function and possibly lead to bradycardia and hypotension by producing beta blockade in patients whose cardiac status is maintained by a high level of endogenous sympathetic activity.

Overdrive suppression. Paradoxically, direct electrical pacing of the ventricle at a rapid rate may restore synchronous contraction. The measure is

usually considered only for patients with intractable ventricular tachyarrhythmias unresponsive to repeated cardioversion and suppressant drug therapy. Insertion of the pacing wire should be performed by an experienced cardiologist.

Stimulant Therapy

When asystole or bradycardia is observed on the ECG, stimulant drugs are administered. Severe acidosis and/or hyperkalemia, however, will make it virtually impossible to restore cardiac action.

Atropine. Excess vagal activity may contribute to bradycardia, heart block, or both. Administration of atropine is recommended for most or all patients. The dose is 1.0 mg intravenously; it should be given rapidly, since slower infusions or lower doses can paradoxically produce vagal stimulation. It is increasingly recognized that atropine is not without hazard. In some patients atropine has produced excessive cardioacceleration, increased cardiac work, and ventricular tachyarrhythmias.

Stimulant drugs. Several drugs are available which produce direct myocardial stimulation. They are usually given successively into a central venous line by bolus injection. If no response is obtained or a central venous route is not available, the same doses may be repeated by direct intracardiac injection.

1. *Epinephrine*, 0.5 to 1.0 mg every 5 minutes.
2. *Calcium salts*, of which several are commercially available in 10% solution. Appropriate doses, providing 4.5 to 6.8 mEq of calcium, are: 5 ml of calcium chloride, 10 ml of calcium gluconate, or 10 ml of calcium gluceptate.
3. *Isoproterenol*, 0.2 mg. This can also be given as a solution of 2.0 mg mixed in 250 to 500 ml of 5% dextrose in water, infused at 2 to 20 μ g/minute.

Ventricular pacing. Failure of the above measures to initiate cardiac action is prognostically grave. Ventricular pacing using a transvenous or transthoracic pacing wire inserted into the right ventricle may succeed in restoring electrical activity. The procedure should be performed by a cardiologist if possible.

Treatment of Hypotension

Occasionally, CPR restores normal electrical activity of the heart without restoring normal cardiac output, blood pressure, and perfusion of vital organs. This so-called "electrical-mechanical dissociation" suggests either that intravascular volume is greatly depleted, or that myocardial damage is so severe as to preclude adequate contractile force.

Volume repletion. The adequacy of intravascular volume relative to the heart's ability to handle the volume load can be assessed by measurement of pulmonary artery "wedge pressure" (PAW). Central venous pressure is also useful but somewhat less reliable. If PAW pressure is low, then intra-

venous fluid and colloid are administered in sufficient amounts to restore normal wedge pressures. Failure of volume repletion to restore cardiac output suggests that myocardial damage is severe. Although the prognosis at this point is unfavorable, a trial of vasopressor drugs is indicated.

Pressors. Vasopressor agents are given by continuous intravenous infusion at a rate sufficient to maintain systolic arterial pressure at 90 to 100 mmHg. A large number of drugs are available, but physicians need to be familiar with only a few. The following agents are the most widely used; the indicated dose is mixed with 500 ml of 5% dextrose in water and given by a well-controlled infusion.

1. *Norepinephrine*, 4.0 mg.
2. *Metaraminol*, 200 mg.
3. *Dopamine*, 500 gm.

Corticosteroids. If all other measures fail to restore adequate circulation, a pharmacologic dose of corticosteroid can be tried as a "last-ditch" effort, although its efficacy is not proven.

SPECIAL SITUATIONS

Occasionally, cardiopulmonary arrest is due to a specific etiology for which relatively specific therapy is available. A few of these situations are described below.

Hyperkalemia

This should be suspected when cardiac arrest occurs in a patient with renal insufficiency. The probability of hyperkalemia is even greater when the patient has been receiving triamterene, spironolactone, potassium supplements, or some combination of these. The ECG will usually reveal asystole, a "sine wave" pattern, or bradycardia with widened QRS complexes.

The usual measures for the treatment of asystolic cardiac arrest are appropriate. Intravenous bicarbonate will lower serum potassium by altering the pH-dependent balance between intra- and extracellular potassium. Calcium is very effective in reversing cardiac toxicity (except in a patient receiving digitalis), and should be given as described above. Intravenous crystalline insulin (10 units) and glucose (50 gm) may also help to shift potassium out of serum and into cells. Eventually, more definitive measures for potassium removal, such as peritoneal dialysis or polystyrene sulfonate resin therapy, will have to be instituted.

Anaphylaxis

Cardiovascular collapse in a young individual following such events as injection of radiographic contrast media, parenteral drug therapy (e.g., iron dextran, penicillin, etc.), a bee sting, etc., is suggestive of an anaphylactic reaction. Intravenous epinephrine (0.5 to 1.0 mg) should be given as soon as possible. Diphenhydramine (50 to 100 mg) and large doses of corticosteroids may also be of benefit.

Drug Overdosage

Accidental or intentional overdosage with one of several drugs can lead to cardiopulmonary arrest for which specific therapy is available.

Opiates. Acute opiate overdosage is sometimes associated with respiratory arrest, hypoxia, and death. Concurrent with the usual resuscitative measures, intravenous naloxone (0.4 to 1.2 mg) should be given as a specific antidote. Repeat doses of naloxone may be needed if respiratory depression recurs.

Tricyclic antidepressants. Life-threatening ventricular tachyarrhythmias sometimes accompany tricyclic antidepressant overdosage. Many reports suggest that intravenous propranolol is a highly effective antidote for such arrhythmias. Intravenous physostigmine (1 to 4 mg), a cholinesterase inhibitor, also appears to act as an antidote in many patients.

CONCLUSION

The coordinated effort of health care professionals utilizing swift and appropriate pharmacotherapy is the keystone of sophisticated cardiopulmonary resuscitation. The likelihood of success depends on the rapid initiation of ventilation and restoration of circulation, and is inversely dependent on the severity of underlying disease or injury. Continued training of resuscitation teams and perfection of emergency service transportation systems should increase the chances of survival in cases of cardiopulmonary arrest, hopefully without sacrificing the quality or dignity of life.

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From the Secretary's Notebook

Summary of Proceedings, Interim Meeting M.M.A. House of Delegates, April 3, 1976 in Bangor, Maine

The Interim Meeting of the M.M.A. House of Delegates was held at the Eastern Maine Medical Center in Bangor on Saturday, April 3, 1976 with an attendance of 49 delegates and alternates and seven guests. Euclid M. Hanbury, Jr., M.D., President of the M.M.A., called the meeting to order, and George W. Bostwick, M.D., Speaker of the House, presided.

1. **Financial Statement of Income and Expenditures for 1975 and Budget Proposed for 1977** was presented by Dr. Richard C. Leck, Chairman of the Budget Committee. Final action on the proposed budget for 1977 will take place at the annual meeting of the House of Delegates on Saturday, June 5, 1976 at the Treadway-Samoset Resort in Rockport.

Several questions on the budget were answered. The allocation of \$10,000 to the **Burn Committee** was questioned and Dr. Hanbury explained the program going to have "burn beds" located all around the State. The "seed money" given to the Committee allowed for the hiring of a secretary and the equipping of an office which is located at the Central Maine General Hospital in Lewiston. A fund drive, with the assistance of the Maine Fire-fighter's group, is underway to pay for the continuing of this program.

In regard to the question of continuing the Journal, Dr. Hanley presented figures of income and expenditures, list of purposes served by the Journal, etc., and this was printed and mailed to the delegates.

Dr. Hanbury remarked that he was amazed, in his travels around the State this year, that the M.M.A. **dues increase** for 1976 was still a "surprise" — despite a near unanimous vote by the House of Delegates last year.

Dr. Leck, also chairman of the Search Committee to find an **Assistant Executive Director**, announced that applicants for the position were discussed with the Executive Committee recently, and Dr. Richard T. Chamberlin hired. Because of his present position with PTO, Dr. Chamberlin will be on a part-time basis at first, gradually working into full time.

2. The preliminary **report of the Committee on Nominations** (printed) was given to each delegate. The report consisted of nominees for vacancies on the standing committees, for President-elect, and for each position to be filled on the M.M.A. Executive Committee (this year, Districts 1, 5 and 6; and

to complete terms for Districts 7 and 9). A **brief biographical sketch of each officer nominee** was sent to members of the House of Delegates.

3. Committee Reports:

a) *Continuing Education* — Dr. Richard T. Chamberlin, Chairman, gave a written report to each member present (copy available on request to M.M.A. office). Dr. Chamberlin also gave a slide presentation of the data taken from the CME forms returned by members of the M.M.A. for the 1975 reporting year (71% of the membership at that time).

b) *Peer Review* — A detailed written report by the chairman, Dr. Chamberlin, was given to the delegates, reviewing peer review activities in Maine — occurring under the auspices of the Pine Tree Organization for Professional Standards Review, Inc. Points emphasized were a) the importance of physician input; b) criteria and peer review; c) continuing problem areas with Federal requirements; and d) the rationale for expansion to ambulatory care and long-term care review. Copies of the admission certification flow chart, continued stay review chart, admission certification flow diagram, model screening criteria format for use in PSRO review and a patterns of treatment chart were given to the delegates and they were urged to take this information back to their county societies. (If anyone would like a copy of this report, it is available from the M.M.A. office.)

c) *Health Care Financing* — Dr. Charles Lightbody, Chairman, reported on activities of this committee over the past few months and mentioned problems being worked on, one of which is a State-wide fee schedule.

d) *Legislation* — The chairman, Dr. Brinton T. Darlington, reported that there is considerable difference in the number and types of bills in this session and he briefly reviewed the ones of most interest to physicians.

4. Five **resolutions** were presented and they were referred to the June House of Delegates for action.

5. Dr. Gardner Moulton and Dr. Fred Lagomarsino, representing the Section on Ophthalmology of the M.M.A., spoke to the delegates about their concern in regard to **medical treatment of the eye** being done by other than physicians. They were also concerned that last year, 44 Maine physicians signed letters and petitions in favor of a bill authorizing optometrists to use diagnostic drugs, etc., and that these letters and petitions have been circulated

to the Massachusetts legislature where a similar bill is under consideration. Drs. Moulton and Lagomarsino were invited to submit a copy of their report to The Journal of the M.M.A. for possible publication.

6. The next **malpractice commission** hearing will be on April 3rd at Bates College in Lewiston reported Dr. Francis Kittredge, our representative on that commission. He hopes to get hearing dates earlier so sufficient notice may be given. Dr. Kittredge reported on their activities to date. Dr. Hanley added that the insurance superintendent of the State is assisting in getting insurance for physicians and the #1 problem is availability, with cost the second consideration.

7. Dr. Hanbury mentioned the possibility of the M.M.A. being asked to assist in the proposed mass inoculation for **Swine Flu** this fall, and in anticipation of this, he asked that each county society send the name of a physician willing to work on this program, directly to Dr. Hanley (P.O. Box 250, Brunswick).

8. Dr. Bostwick, Speaker of the House, announced that the following physicians will be serving on **Reference Committees** for the June meeting: Drs. A. J. Horstman, W. O. Buell, D. P. Cole, E. M. Davis, J. H. Steeves, J. R. Davy, C. F. Manning, D. K. Onion, G. J. Harrison, O. T. Feagin, R. W. Pawle, D. W. Schall, J. A. Smith and T. F. Shields.

Announcement was made of a **Workshop for Medical Directors of Skilled Nursing Facilities** to be held on May 26th in Bangor.

Dr. Bostwick read a letter from Richard D. Upham, President of the Maine Association of Medical Suppliers, urging cooperation from physicians in completing necessary forms for patients which indicate diagnosis and reason why the equipment or item is medically necessary.

9. Adjourned at 4:15 P.M.

PATRICIA A. BERGERON
Secretary-Treasurer

THE MB ISOENZYME OF CREATINE KINASE IN THE DIAGNOSIS OF MYOCARDIAL INFARCTION

Continued from Page 162

pre-existing disease states which may elevate total CK. Quantitative elevation of the MB-CK (>4.0 IU/L) then strongly suggests infarction. In those patients who have had myocardial infarction and CK values have returned to normal, a subsequent elevation of MB-CK may represent the first evidence that further extension of the initial infarct has occurred.

It was of interest to note that the HBD determination offered no additional information over total CK and MB-CK values except for a single patient in whom myocardial damage had occurred several days prior to testing.

It is our opinion that total CK and MB-CK isoenzyme values are sufficient to adequately adjudicate myocardial infarction in those cases where infarct has occurred within 24-36 hours of obtaining the first blood specimen. The HBD may add supportive evidence of possible infarct if necrosis has occurred prior to that time.

ACKNOWLEDGEMENTS

The excellent technical assistance of Rebecca Umayam and Jerome Jordan was greatly appreciated.

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Maine Blue Cross and Blue Shield News

HIGHLIGHTS OF THE AHS ANNUAL MEETING

Eleven Board members were elected and several changes in the corporation Bylaws were ratified at the Maine Blue Cross and Blue Shield Annual Meeting of members in Portland on Wednesday, April 21, 1976.

Reelected to represent subscribers were Joseph S. Jones of South Portland, President of Megquier & Jones Corporation; Woodrow E. Page of Dover-Foxcroft, a retired State employee; Owen S. Estey of Mapleton, President of Potato Meal, Inc.; and Constantine Karvonides of Biddeford, Vice President of Peperell Trust Company.

Hospital trustees reelected to represent health care providers were Lloyd H. Holmes of Portland, President of Holmes Electrical Supply Company; Laurier T. Raymond, Jr., of Lewiston, an attorney at law; and William J. St. Onge of Sanford, Executive Manager of the Sanford/Springvale Chamber of Commerce. Robert W. Hudson of Auburn, an Honorary Board member of Central Maine General Hospital was also reelected to represent health care providers.

Louis A. Asali, M.D., of Scarborough, and John R. Davy, M.D., of Portland, were elected to represent participating professionals. Newly elected to the Board was James L. Fife, M.D., of Brunswick.

Several Bylaw changes were also ratified by the membership, including:

- the expansion of the Board from 31 to 32 members to allow the President of the corporation to be a Board member;
- a change limiting a Board member's tenure to three consecutive three-year terms;
- the addition of a clause that ensures that directors with unjustified poor attendance would be removed from the Board;
- the establishment of an honorary Board of Directors made up of prior Board members who had served with distinction;
- an increase in the number of Board meetings from three to six a year;
- a provision allowing the Chairman to call additional meetings; and
- a change requiring that Directors be given two weeks' notice before a vote on any amendment to the Bylaws could be taken, as well as requiring an affirmative vote of at least 2/3 of those Directors present and, in any event, not less than a majority of the full Board.

The Board also publicly honored six employees for giving thirty years of service to the organization. They were Doris Allen, Evelyn Armstrong, Lillian Jennings, Mary Mason, Richard Nellson, President, and R. Weston Pierce, Senior Vice President.

News, Notes and Announcements

New England Regional Emergency
Medical Services
October 6-8, 1976 — Portland, Maine

Continuing Medical Education Requirements State of Washington

The State Board of Medical Examiners has scheduled a public hearing in Seattle April 23 at which time it will consider adoption of mandatory continuing medical education rules for physicians.

Kenneth C. Diehl, Administrator of the Division of Professional Licensing, Department of Motor Vehicles, said the hearing will be held in the Spanish Ballroom, Olympic Hotel, Fourth and Seneca, Seattle, beginning at 1:30 p.m.

Diehl explained that the State Board was authorized to establish rules for mandatory continuing education by House Bill 788 passed by the Legislature in 1975.

The new rules would affect about 10,000 physicians licensed in Washington State. Diehl said of that total about 6,000 are in active practice. The remainder are either retired or living in other states.

The proposed rules would call for 50 credit hours of continuing education each year.

Diehl said there are several ways a physician could satisfy the requirement. Included are continuing medical activities with or without accredited sponsorship, teaching, publication of papers or books and self-assessment or self-instruction.

The rules would require that credit hours be earned in three of the categories.

Diehl added that mandatory continuing medical education for physicians has been instituted in 10 or 12 other states and will continue to spread.

He noted that most practicing physicians already meet the requirement.

For additional information contact Ken Mark, Information Officer, Professional Licensing Division, Business & Professions Administration, P. O. Box 649, Olympia, Washington 98504 (206) 753-4091.

Postgraduate Education for Pediatricians and Obstetricians

The Maternal and Child Health Program of the University of California School of Public Health at Berkeley announces postgraduate programs for pediatricians and obstetricians in the field of Maternal and Child Health and Family Planning. Program areas available at the present time include nine-month programs in Maternal and Child Health, in the Health of the School-Age Children and Youth, and Day Care and the Preschool Child. Twenty-one month programs in Care of Handicapped Children and Comprehensive Health Care, and a thirty-three month program in Perinatology are also available. These programs all lead to the degree of Master of Public Health, and tax-exempt Fellowship support is available.

Applications are now being accepted for the group entering September 1977. For information, write to Helen M. Wallace, M.D., School of Public Health, University of California, Berkeley, California 94720.

Necrologies

FOSTER C. SMALL, M.D.

1885-1976

Dr. Foster C. Small, 90, of Belfast, Maine, President of the Maine Medical Association from 1950-1951, died at a Belfast hospital on March 2 following a long illness.

Born in Swanville, Maine on December 4, 1885, he was the son of Charles E. and Hattie E. M. Small.

Dr. Small taught school in Searsport for approximately six years and then for several terms in Swanville, where he was superintendent of schools for some time. At an early age, he had set a goal at becoming a physician, and in 1912 he was graduated from the University of Vermont Medical School, third in his class. He returned to the Belfast area and opened his medical practice, affiliated with the late Dr. Eugene Tapley at the Bradbury Memorial Hospital. He then joined the surgical staff of the Waldo County General Hospital, where he and the late Dr. Carl Stevens were for many years the only surgeons.

Dr. Small's dedication to the medical profession is well known. He had traveled thousands of miles by horse and buggy, homemade snowmobile, Model T Ford, and various other modes of transportation, when necessary to attend to his patients and the needs of his community.

An honorary member of the Waldo County Medical Society and the Maine Medical Association, Dr. Small received a 50-year pin in 1962, a 55-year pin in 1967 and a 60-year pin in 1972. He served as Councilor for the Fourth District of the M.M.A. in 1947-1948, Council Chairman in 1948-1949, President-elect in 1949-1950 and President in 1950-1951. Dr. Small was also a member of the American Medical Association.

Survivors are one nephew, George E. Small of Searsport; and a niece, Mrs. Earl Dakin of Kentucky.

PAULINE G. STARKS, M.D.

1911-1976

Dr. Pauline G. Starks, 64, of Pemaquid Point, Maine, died on March 20.

Born in Winsted, Connecticut on June 4, 1911, she was the daughter of Harrie E. and Gertrude W. Starks.

Dr. Starks was graduated from Wellesley College in 1934 and received her medical degree from Tufts University School of Medicine in 1943. She interned at the Central Maine General Hospital in Lewiston and the New England Hospital for Women

and Children, Boston in Pediatrics; and served residencies at the Central Maine General Hospital in Pediatrics and the Hartford Hospital, Connecticut in Anesthesiology.

Specializing in Anesthesiology, Dr. Starks practiced in Lewiston from 1949 to 1956, Putnam, Connecticut from 1958 to 1971 and then located in Pemaquid Point.

Dr. Starks was a member of the Lincoln-Sagadahoc County Medical Society and the Maine Medical Association.

ADRIAN H. SCOLTEN, M.D.

1891-1976

Dr. Adrian H. Scolten, 84, of Hendersonville, North Carolina, died on March 21 at a local hospital after a short illness.

He was born in Prairie View, Kansas on September 6, 1891, son of the Reverend Dirk and Alice Scolten.

Dr. Scolten was graduated from the University of Wisconsin and received his medical degree from Washington University Medical School in 1931. He interned at Boston City Hospital and served residencies at the University of Pennsylvania Hospital and the Bert Shirley Hospital in Detroit, Michigan. He located in Portland, Maine in 1934, practicing Dermatology until his retirement in 1975, when he moved to North Carolina.

He was well known for his many letters to the editor to the Portland newspapers, as well as *The Journal of the Maine Medical Association*, on such subjects as his opposition to marijuana and fluoridation of drinking water.

In 1948, he was a Democratic candidate for the U.S. Senate,

running against the now retired Senator, Margaret Chase Smith. Dr. Scolten was recently named to appear as one of the Notable Americans of the Bicentennial by the American Biographical Institute.

A senior member of the Cumberland County Medical Association and the Maine Medical Association, Dr. Scolten was also a member of the American Medical Association, the American Academy of Dermatology, the American Academy of Allergies and the New England Psychiatry Society.

Mrs. Scolten, the former Dorothy M. Walstad, died on March 11.

Surviving are three brothers, Alfred of Hendersonville, the Reverend George B. of Wayne, New Jersey and the Reverend Walter A. of Greenwich, New York; two sisters, Mrs. Mamie H. Muyskens of Holland, Michigan and Mrs. Alice E. Van-Zoeren of Scotia, New York.

ISAAC NELSON, M.D.

1904-1976

Dr. Isaac Nelson, 71, of Greenville, Maine, died at a Bangor hospital on April 10.

He was born in New York City on July 30, 1904, son of Hyman and Sara S. Nelson.

Dr. Nelson was graduated from the City College of New York, Columbia University and received his medical degree from Long Island College Medical School in 1927. He interned at St. Peter's Hospital in Brooklyn, New York and practiced in

Brooklyn for thirty-four years. In 1954, he located in Greenville.

He was a senior member of the Piscataquis County Medical Society and the Maine Medical Association.

Surviving are his widow, Amy Weldon Nelson of Greenville; one daughter, Mrs. Ina Jane Gerow of Milo; one son, Craig of Farmingdale; one sister, Mrs. Shirley Leff of Lynnbrook, New York; and five grandchildren.

FRANCIS X. MACK, M.D.

1921-1976

Dr. Francis X. Mack, 55, of Portland, Maine, Director of Anesthesiology at the Mercy Hospital for more than twenty years, died on April 20 at a local hospital after a short illness.

Born in Milton, Massachusetts on January 7, 1921, he was the son of William F. and Mary G. Mack.

A graduate of Boston College, Dr. Mack received his medical degree from Tufts University School of Medicine in 1945 and served in the U.S. Army Medical Corps for two years as a 1st Lieutenant. He interned at the Boston City Hospital and served a residency at the Veterans Administration Hospital in Dallas, Texas. Dr. Mack was affiliated with the Boston City Hospital, the Massachusetts Memorial Hospital and various Veterans hospitals. In 1953, he located in Portland.

Dr. Mack was an affiliate member of the Cumberland County Medical Society and the Maine Medical Association. He was

also a member of the American Society of Anesthesiologists, past president of the Maine Society of Anesthesiologists and was on the executive committee of the Mercy Hospital for seven years.

Surviving are his wife, Barbara Kearns Mack; nine daughters, Mrs. Peter K. McDermott of Rochester, New York, Patricia L., Mary J., Barbara, Justine M., Michelle A., Kathleen M., Claire J. and Jennifer Mack, all of Portland; five sons, William F., Thomas J., Francis X., Jr., Christopher E. and Joseph F. Mack, all of Portland. Also surviving are three sisters, Mrs. John Patch of Placentia, California, Sister Adrienne Marie of Norwalk, Connecticut and Mrs. A. Joseph Dowd of Glen Cove, New York; two brothers, Daniel of Salem, New Hampshire and William of Swampscott, Massachusetts; a granddaughter, several nieces, nephews and cousins.

HENRY M. HOWARD, M.D.

1896-1976

Dr. Henry M. Howard, 79, formerly of Rumford, Maine, where he had practiced for over fifty years, died on April 23 at the Poet's Seat Nursing Home in Greenfield, Massachusetts. His summer residence was in Rangeley.

He was born in Andover, Maine, on September 5, 1896, son of Marshall and Mary Glover Howard.

Dr. Howard was graduated from Andover High School and Kents Hill Academy, attended Bowdoin College and received his medical degree from Bowdoin Medical School in 1921. He interned at the Maine Eye and Ear Infirmary and the Waterbury General Hospital in Connecticut.

During World War I, he served in the U.S. Navy and with the U.S. Army Medical Corps in World War II, retiring with the

rank of Major.

An honorary member of the Oxford County Medical Society and the Maine Medical Association, he received a 50-year pin in 1971 and would have been eligible for his 55-year pin at the June 1976 annual session. Dr. Howard was also a member of the American Medical Association and was a staff member of the Rumford Community Hospital, the Central Maine General Hospital and the Maine Medical Center.

Surviving are two daughters, Mrs. Robert Peck of Lenox, Massachusetts and Dr. Ann F. Howard of Greenfield, Massachusetts; a sister, Mrs. Guy Akers of Weston, Massachusetts; and five grandchildren.

County Society Notes

Kennebec

The Kennebec County Medical Association met at the Augusta Civic Center on January 22, 1976, with twenty-six members and guests present. The meeting was called to order by the President, Dr. Joseph J. Hiebel. Minutes of the previous meeting were read and accepted. Report of the Nomination Committee was made and the Secretary was instructed to cast one ballot. The officers are as follows:

President: Dr. James C. Hayes, Augusta
Vice-President: Dr. Richard E. Barron, Winthrop
Secretary-Treasurer: Dr. O. Thomas Feagin, Augusta
Council: Drs. Valentine J. Moore and John W. Towne, both of Waterville
Delegates to the M.M.A. House of Delegates: Drs. George I. Gould, Richmond, Terrance J. Sheehan, Augusta, Howard H. Milliken, Hallowell, Earle M. Davis, Raymond E. Culver and Anthony Betts, all of Waterville. Alternates: Drs. Ulrich B. Jacobsohn, Farmingdale, John H. Shaw and Harry M. K. Peddie, both of Augusta, Charles E. Towne, Antoine A. Atallah and J. Alfred Letourneau, all of Waterville

A vacancy on the Council does exist, the Nominating Committee being unable to arrive at a nominee at this point in time. They will present a nominee at the next meeting.

Old Business: Dr. William E. Schumacher has asked Dr. Feagin to report to the members that the bylaws were in the process of being typed and would be sent out. He did wish some comments from the members on a couple of points. Namely: should the term of office be two years instead of one. There seemed to be a basic sentiment that the President, Vice-President, and Secretary-Treasurer's term of office should be one year and that the Council should remain three years. The next question was the timing of the annual meeting, which the Council had felt should be in May and the membership seemed to be agreeable to this change in the bylaws.

New Business: The applications of Drs. H. Alan Hume and Romulo Beltran were read. The Treasurer's report was presented and accepted. Dr. Hayes, the new President, introduced Mr. Fletcher Bingham of the Maine Hospital Association who presented a most informative talk on the problems facing the Maine hospitals in the near future, some of which included the interest of unions in hospitals, problems of hospital financing, and problems in Health Planning. The talk was most appreciated by the membership.

The Kennebec County Medical Association met on February 19, 1976 at the Silent Woman Restaurant in Waterville, Maine, with 31 members and one guest present. Following a cocktail hour, the meeting was called to order at 8:00 p.m.

The minutes of the previous meeting were read and accepted.

Communications were received from Mr. Philip Judd of the Medical Care Development, Inc. requesting sponsorship of the Association for a conference on use of physicians' assistants. There was some discussion as to whether the Association wished to appear as a sponsor since it would imply approval of physicians' assistants. It was suggested that Mr. Judd might come to the Association and discuss with the members what the nature of this affair would be, but at this point in time, the members did not wish to sponsor the conference as requested.

A letter from Mr. Philip DeMaria of the Maine Heart Association was read in which he requested the Medical Association to endorse a blood pressure screening program in the Waterville area and the Association agreed to endorse this program.

A letter from Dr. H. Alan Hume regarding Statewide meeting on emergency medical services was read and the members were invited to attend the meeting on February 24, 1976.

The members were informed of a memorandum from Dr. Hanley regarding the malpractice commission hearing in Waterville on February 23rd.

A letter was received from the Philadelphia County Medical Society stating that Dr. Robert Wise was a member in good

standing there and he is transferring his membership to the Kennebec County Medical Association.

There was no new business.

Old Business:

The application of Dr. H. Alan Hume was favorably acted upon and he is welcomed into the membership. The application of Dr. Romulo Beltran had to be deferred due to the fact that the application was incomplete in one respect.

Dr. Schumacher presented a report of the Bylaws Committee, which consisted of a new draft of the Bylaws. Copies were distributed to the members present and will be distributed within the next month to the remaining members of the Association so that the Bylaws can be voted on at the March meeting.

Finally, Dr. Hayes introduced Dr. H. Alan Hume, the new Director of the Emergency Medical Services, who discussed with us the plans for the Kennebec-Somerset Region in regards to emergency care. Members questioned him vigorously about several aspects of ambulance service, etc., and a lively discussion was held.

The meeting adjourned approximately at 9:15 p.m.

O. THOMAS FEAGIN, M.D., Secretary

Washington

The regular meeting of the Washington County Medical Society was held on February 9, 1976 at the Staff Lounge, Calais Regional Hospital, Calais, Maine, with thirteen members and guests present.

Meeting opened under the direction of Dr. G. Bernard Shaw, President of the Society.

I. Minutes of the last meeting were read and approved.

II. (a) Kathryn Calder of the Washington County Health Plan, East Machias, Maine spoke relative to the Rural Health Initiative Plan for which they have submitted an application. This plan would fund three additional physician extenders for the county, including either MEDEXS' or Nurse Practitioners'. Initially, there was some thought of getting a Nurse Mid-wife; but this was not thought to be too practical. This plan will also include transportation of covered people from their home to hospitals, clinics and to physicians, to improve the health status through health prevention program. (b) Jane Weil, Field Supervisor of the Washington County Handicapped Children Program, then spoke on their program. This has just been funded by a grant for the Bureau of Education of the Handicapped of the U.S. Office of Education. She stated the purpose of the grant to the Washington County Program is to establish a home base program designed to meet the needs of the pre-school children, for their physical, mental and emotional problems. They have hired seven home teachers who have completed a three-week pre-service training program. These teachers will be working on a weekly basis with the children and their family members, who have been referred to the program. Working with Ms. Jane Weil is Field Supervisor Ms. Sharon Southerland. The home teachers will be working under the supervision of Ms. Southerland.

III. (a) Application of Dr. David Eitel of East Machias, Maine was approved. He was made a member of our Society. (b) Application of Dr. Maria T. Zientara of Calais, Maine was approved. She was made a member of the Society. (c) Application of Dr. Jonathan Glen of Portsmouth, New Hampshire was approved and he is to be made an honorary member until he can be contacted and to find out whether or not he would want to join the Maine Medical Association or would prefer to join the New Hampshire Association.

IV. The subject of Continuing Medical Education was brought up with five members to be notified that they have not reported their Continuing Education for 1975.

V. Dr. Robert G. MacBride was appointed Delegate to the Maine Medical Association, with Dr. Donald M. Robertson appointed as Alternate Delegate.

VI. The obituary of Dr. Perley J. Mundie has not been published as yet. Mrs. Bergeron, Secretary of the M.M.A., was

contacted and the obituary will be published at a later date.

VII. A discussion of a patient who was reluctant to pay his physicians' and hospital bills, since he felt that he had not properly been cared for. This particular patient has been contacted by the President, and the matter will be turned over to the Grievance Commander.

VIII. (a) Dr. Mark E. Battista, Lubec, Maine has been appointed to the Bylaw Revision Committee, in place of Dr. Carl K. Aselton, Jr., who has moved. (b) Dr. Christopher D. Mace has been appointed as Chairman of the Diabetes Committee, in place of Dr. Rowland B. French, who has resigned.

IX. Discussion of the Condor Trust. Physicians warned of this organization; it is not licensed to transact insurance business in this State.

X. (a) Letter read from Dr. Euclid M. Hanbury, Jr. in regard to H.S.A. Board of Trustees. It is felt that the Medical Society had apparently acted too late to elect a member, who they desired, to be a member of the Board of Trustees. (b) A letter was also read from Rev. Michael L. Carlson re: Citizens Commission on Human Rights re psychiatric violations. (c) A letter also read in regard to Manpower Legislature.

XI. Some discussion as to the Mason-Stone controversy. It was felt that since both physicians are no longer members of the Society that the Society would not be concerned and Mr. Cragin would be so notified.

XII. Dr. Karl V. Larson was nominated as Executive Committee member from Washington County when the next vacancy comes up from Hancock, Washington and Waldo Counties.

XIII. Dr. Robert G. MacBride spoke on a School Based Dental Prevention Program for the county, which is being undertaken by the Child and Youth Board of Washington County. They have applied for funding through the State Dept. of Health and Welfare to initiate School Based Prevention Programs at the elementary level on a county-wide basis. All physicians agreed that this program was badly needed, since the youth of the county, for several years, have had marked dental neglect.

XIV. The Society also approved the payment of the bill for

Attorney Charles Cragin III for the amount of \$237.50 for the Stone-Mason controversy.

XV. Dr. Hazen C. Mitchell of Calais, Maine said that Dalhousie Medical School should be approached to see if they would admit a certain number of subsidized students from Maine into the college. The college will be contacted as well as Dr. David Smith.

The regular meeting of the Washington County Medical Society was held in the Staff Lounge, Down East Community Hospital, Machias, Maine on March 29, 1976, with six members and one guest present. Meeting opened under the direction of Dr. G. Bernard Shaw, President of the Medical Society.

I. Minutes of last meeting read and approved.

II. *Old business:*

a. Dr. Christopher D. Mace, Diabetic Chairman.

b. Dr. Mark Battista, Bylaws Committee.

III. *Communications:*

1. Letters from Dr. Smith and Dr. Chamberlin, Re: Subsidizing Medical students to attend Dalhousie Medical College. Action will be deferred until some definitive ruling is made.

2. Letter from Blue Shield asking if one of their members could speak at one of our meetings. It was decided it would be wise to invite one of their officials to speak.

3. Letter from Attorney Cragin in regard to the Mason-Stone controversy. Since neither are members of our Medical Society, it was felt no longer a concern of our Society.

IV. Peter J. Cannon, Administration Assistant of Down East Health Services of Calais, Maine, spoke on Early and Periodic Screening, Diagnosis and Treatment. He stated they were funded, at present, to send "out-reach workers" to contact new Medicaid recipients from ages 0-21. They would be notified of the service available and asked if they would want to take advantage of this service. If so, they would be screened by the out-reach workers and by the nurse and referred either to their family physician or a Pediatric Nurse Associate. Screening will consist of health history; development appraisal; what immunizations

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they had received; physical growth; physical appraisal, including also blood pressure; hct.; hgb.; lead screening; vision and hearing.

V. EPSDT, cont.: Follow-up appointments will be made and transportation will also be arranged for patients referred to physicians or clinics. Clinics may also be set up, if arrangements can be made. There also will be referrals for dental care. Members of the Society questioned the feasibility of this. The Society felt there was a tremendous need for dental referral. The main problem, however, is the lack of enough dentists to carry on this type of service. Some of the physicians reported that the dentists they talked to were not too happy with taking Medicaid patients, since so many of them in the past had failed to keep appointments.

VI. Meeting adjourned.

KARL V. LARSON, M.D., *Secretary*

Cumberland

The 401st meeting of the Cumberland County Medical Society was opened by the President, Dr. Robert E. McAfee, at approximately 8:15 p.m. at Valle's Steak House on February 19, 1976, and 93 members were in attendance. The minutes of the previous meeting were omitted.

Applications for Membership:

First reading: Drs. Edward C. Andrews, Jr., Thomas F. Clafey and Stuart G. Gilbert.

Second reading: Drs. Dermot N. Killian, Edward A. McCarthy, Jr. and Carl J. Morrison.

It was moved, seconded, and voted that the latter three names be accepted for membership in the Cumberland County Medical Society.

Announcements:

There were announcements and points of information on seven items:

1. The Tel-Med System for patient education will be operational in the summer of 1976.

2. We were warned about the Condor Trust, a fraudulent scheme to provide malpractice insurance at cut rates.

3. A regional conference on physicians' assistants was announced to be held on Wednesday, March 24, 1976 at the Maine Medical Center.

4. The Health Systems Agency Board — Dr. John F. Gibbons has been named as an additional member of this Board from Southern Maine.

5. Medical School — Dr. McAfee made some preliminary remarks concerning a proposal which would result in sending forty students from the State of Maine to medical school each year.

6. National Advisory Committee on Ethics — The genesis of this Committee explained by Dr. McAfee.

7. Senate Bill #2697 — The AMA is taking immediate action to defeat the proposed bill by Senator Kennedy which would result in the fining of a physician \$10,000 each time he prescribes a drug for an indication not listed in the package insert of the drug.

New Business:

1. Continuing Medical Education — A proposal was discussed, and it was voted to develop a resolution to be brought before the House of Delegates in June.

2. Consumer Directory — A Committee was formed to meet with Joanne Amerling, local T.V. consumer representative, to discuss the matter of a consumer directory.

3. Medical Malpractice — Dr. McAfee reported on the results and subjective feelings derived from a public hearing held by the Malpractice Commission of the State of Maine on February 17, 1976 at the Law School in Portland. Basically, there was a strong note of cooperation between the lawyers and physicians running through the thread of the discussion at the meeting.

The meeting was adjourned at approximately 10:15 p.m.

WESLEY J. ENGLISH, M.D., *Secretary*

Lincoln-Sagadahoc

The regular monthly meeting of the Lincoln-Sagadahoc County Medical Society was held at The Ledges in Wiscasset, Maine on March 16, 1976 in a howling blizzard.

Seven members and three guests enjoyed dinner and dispensed with the reading of the minutes of the last meeting.

Dr. David S. Hill opened the meeting at 8:25 p.m. by allowing Dr. Paul H. Dumdey to introduce the speaker, Dr. H. Alan Hume, the State Director of Emergency Medical Services, who explained his work and entered into a spirited dialogue with the members.

The meeting was adjourned at 9:40 p.m.

GEORGE W. BOSTWICK, M.D., *Secretary*

Penobscot

The monthly meeting of the Penobscot County Medical Society was held on February 17, 1976 at the Pilot's Grill in Bangor, Maine. The meeting was opened by the President, Dr. Thornton W. Merriam, Jr., and the minutes of the January 1976 meeting were read and approved.

Several communications were received during the previous month, and the following were brought to the attention of the membership. A copy of the letter written by Frank M. Hogerty, Jr., Superintendent of Insurance to Dr. Dan Hanley, alerting the Maine Medical Association to an organization called the "Condor Trust" of Vancouver, British Columbia. This organization is writing malpractice insurance and has solicited individual members of the Association. This organization is considered suspect and is presently under investigation in Canada. A second letter from Frank M. Hogerty, Jr. was received in response to a letter written by Dr. Herbert C. Gilman regarding the availability of malpractice insurance. This letter stated that there did not appear to be a malpractice insurance crisis within the State of Maine and that insurance was available for all doctors including new doctors arriving in the State. It was pointed out that this letter was in some conflict with recent experience on the part of some individuals in our local area. A letter was received from Blue Cross and Blue Shield requesting an opportunity to speak to the Society

Reminder to M.M.A. Members

CONTINUING MEDICAL EDUCATION ACTIVITY REPORT

The bylaws of the Maine Medical Association were amended in June of 1973 as follows: Chapter I, Section 11, — "Each member of the Maine Medical Association shall be required to report his activities in continuing medical education every year according to a format provided by the Committee on Continuing Medical Education."

Only active, dues-paying members are required to report this year.

Please fill in your activity report promptly and return to the M.M.A. office, P.O. Box 250, Brunswick, Maine 04011.

regarding Blue Shield payments, the URC contract, etc. After some discussion, it was noted that the Society not invite a representative from Blue Shield to address this organization at this time. Finally, it was noted that letters of response had been received from Representative Cohen, Senators Hathaway and Muskie, and Commissioner David Smith with regard to our recent letters objecting to the Health Systems Agency and its composition.

There was no old nor new business brought before the meeting.

Scientific portion of the meeting was a presentation by Dr. George O. Chase on the subject of Malignant Melanoma. Dr. Chase presented a series of excellent slides depicting the various classifications of Malignant Melanoma. Of equal importance and entertainment was his commentary during the presentation.

As there was no further business, the meeting was adjourned.

PHILIP G. HUNTER, M.D., *Secretary*

Androscoggin

The monthly meeting of the Androscoggin County Medical Association was held at Steckino's Restaurant in Lewiston, Maine on March 18, 1976. The meeting was called to order by the President, Dr. Stanley D. Rosenblatt, at 8:00 p.m.

The minutes of the January meeting were dispensed with, with the exception of Miss Giguere's salary increase included.

There was an announcement regarding the forthcoming meeting of the House of Delegates of the Maine Medical Association. Any resolutions or problems on the minds of the membership were requested. No new business was proposed.

Dr. Charles A. Hannigan then presented the President of the Maine Medical Association, Dr. Euclid M. Hanbury, Jr. Dr. Hanbury gave a formal presentation at which time he commented on the pending legislation regarding the nursing practice act, physician assistants and the use of Lidocaine. He also commented on the Maine Medical Lobbyist. He also urged the Association to police their own ranks. He did mention a new legislation which guaranteed due process and at the same time insuring immunity. Following the formal presentation, there was a question and answer period. There was a discussion regarding the assistant executive director and a formal announcement regarding this will be made at the House of Delegates meeting on April 3rd. There was a question regarding the Maine Medical Association's role in the HSA. Dr. Hanbury commented that the

Association was being beaten down in most attempts to submit any worthwhile input. There was a question regarding Blue Shield policy in regards to the difference in hospital and office payments and apparently there are plans for further investigation into this problem. Following this discussion, the meeting was adjourned.

STANLEY D. ROSENBLATT, M.D., *President*

Waldo

The meeting of the Waldo County Medical Society was held at Jed's Restaurant in Belfast, Maine on March 24, 1976.

Members present were Drs. Knuuti, Torrey, Caswell, Smith, Childs, Hanbury and Jollie. In addition, Ms. Laura Franciose of the Blue Cross/Blue Shield of Maine was present.

A business meeting was conducted prior to the discussion by Ms. Franciose. The minutes of the previous meeting were read and accepted. The treasurer's report was read. There were expenditures of \$31.50 for flowers for Dr. Small's funeral and receipt of \$200.00 in annual dues. This left a balance of \$566.98, in addition, there is \$120.00 in dues outstanding.

There was no old business.

New business: Dr. Smith briefly discussed the form to be completed for the M.M.A. in regard to continuing education. This form is termed the continuing education activity report and is to be returned to the Maine Medical Association.

Following this, Ms. Franciose spoke about various topics pertinent to new programs offered by Blue Cross/Blue Shield. She also answered general questions about the organization.

Meeting was adjourned.

JOSEPH A. SMITH, M.D., *Secretary*

Psychiatrist vacancy at VA Center, Togus, Maine. Located 5 miles from capitol, amidst evergreen mountains, sparkling lakes and rockbound coast, open highways and clean cool air, unsurpassed for its four seasons recreation resources. Salary \$32,000 to \$37,800 plus bonus and other excellent benefits. Call or write Chief, Psychiatry Service, Tel. (207) 623-8411, ext. 311 or 404. State license in any one of the 50 United States required. An Equal Opportunity Employer.

Letters to the Editor

To the Editor:

The American Optometric Association is a powerful organization whose goal is to have the optometrist replace the physician as the primary eye care practitioner, thus denying the ophthalmologist the right to practice general ophthalmology and relegating him to the position of secondary and tertiary eye physician. If this goal is attained, it would also prevent the family practitioner, pediatrician or any other practitioner from treating eye disease without consultation with an optometrist.

To help achieve this goal, the AOA has budgeted six million dollars for 1976 to influence legislation in its favor. It employs three more lobbyists in Washington, D.C., than does the entire American Medical Association. Its schools are flooding the country with optometrists.

On a state by state basis, it has amended the optometry laws to define optometry in such a way that an ophthalmologist is allowed to practice only as an exception to these laws. In several states, it has been successful in getting legislation enacted that allows optometrists to use "diagnostic drugs," Maine being one of these states. In West Virginia, it was successful this year in getting legislation allowing optometrists to use therapeutic drugs in the treatment of eye disease. This bill as originally introduced would have allowed optometrists to perform eye surgery, but this section was deleted in the final bill. It has been successful in

many states in amending health legislation in such a way that a physician may not utilize the services of his medical assistants in examination and treatment of the eyes. It is attempting to convince comprehensive health care planning organizations that the optometrist should be designated the primary eye care practitioner.

In June 1974, the Maine Medical Association adopted the following resolution:

WHEREAS, the administration or prescription of drugs or medications, even topically for the eye or its adnexa, or any surgical procedure including the removal of foreign body from the eye or its adnexa, constitutes the practice of medicine, and

WHEREAS, Optometrists have not passed the examination required by the Medical Practice Act for the practice of Medicine in this State,

THEREFORE BE IT RESOLVED that the Maine Medical Association, for the purpose of conservation of vision and for safe and proper examination and prescription of patients, opposes the use of drugs or medications by Optometrists, or surgery by Optometrists, including the removal of any foreign

body from the eye or its adnexa, and

THEREFORE BE IT FURTHER RESOLVED that the Maine Medical Association direct its legislative committee to oppose legislation giving statutory permission for such practice.

During the 107th Legislature, State of Maine, 1975, Legislative Document No. 556, an act authorizing optometrists to use diagnostic drugs — topical anesthetic, cycloplegic, mydriatic, and miotic — was introduced. At the hearing before the Joint Standing Committee on Health and Institutional Services introduced as evidence were letters and petitions in favor of such legislation signed by forty-four Maine physicians, all members of the Maine Medical Association! This bill was enacted by the Legislature and signed into law by the Governor. Cycloplegics and miotics were deleted from the final bill.

In the opinion of the ophthalmologists of the State of Maine, the lobbyist employed by the Section of Ophthalmology, and several legislators, this bill would not have passed except for the endorsement of these forty-four Maine physicians. It made no difference that four of these physicians had also signed petitions in opposition to the bill, and several had sent letters recanting their original endorsement.

In 1975, similar legislation was introduced in the Legislature of the State of Massachusetts. This legislation was not enacted. In 1976, this bill has been re-introduced. The optometrists of Massachusetts have presented each legislator with a multiple page "packet" of information in support of the legislation. Included in this "packet" are the letters and petitions signed by these forty-four Maine physicians. It is interesting to note that there are no such letters and petitions signed by a Massachusetts physician.

GARDNER N. MOULTON, M.D.
Chairman
Section on Ophthalmology
Maine Medical Association
April 3, 1976

To the Editor:

RE: NURSE PRACTITIONERS

I have recently taken the position of Director of the Family Nurse Associate Training Project of the University of Maine School of Nursing — Portland/Gorham. I am eager to know and serve the needs of physicians of all specialties and types of practices in the State who have an interest in relating to a nurse in the extended primary care role. Our project requires nurse trainees to be sponsored by a physician who will supervise and participate in the training program. The FNA is trained in a full-time 6 month didactic and clinical teaching phase in the Portland/Gorham area during which the trainee continues to have monthly clinical experience sessions with the sponsoring physician. The intensive course and clinical work is preceded by a 6 month preparatory phase and followed by a 6 month field experience phase during which the trainee works with the sponsoring physician and attends seminars monthly.

A new class will start in July and we are now receiving applications from nurses — sponsors.

Please contact me for further information.

GEORGE L. PAUK, M.D.
Project Director
Chisholm House
233 Western Promenade
Portland, Maine 04102

To the Editor:

I am deeply concerned about the lack of knowledge of physicians, laymen and the paramedical, on all aspects of insect allergy. This lack of knowledge will result in needless deaths. (1) Physicians need to know of the dangers of reactions. (2) Laymen desperately need to recognize the reactions to insects, especially those which forewarn of a possible fatality from a subsequent sting. They need to realize that first aid medication (i.e., an insect sting kit), as well as hyposensitization, is available and necessary.

Insect allergy has been a very special interest of mine for at least twenty years — especially the clinical aspect of insect allergy. As you know, I have written a book, as well as articles, chapters for medical books, and have lectured to numerous medical associations on this subject. In addition, because of announcements I placed in various medical journals, I have received from physicians scores of case reports of patients who have had reactions to biting and stinging insects, together with the results of hyposensitization, if attempted. In my medical practice, I have seen many insect allergy patients and have received many letters and telephone calls from physicians, asking for my advice on the management of their insect allergy patients.

I continue to be amazed by the skepticism of some physicians that an insect sting can cause death. From personal knowledge, patients who have received fatal stings have often had their symptoms misdiagnosed as being caused by acute myocardial infarction.

In taking the past history of a new patient who comes to me with a chief complaint of asthma, eczema, etc., I frequently find that he has experienced a severe reaction to insects, also. The family history quite often reveals that another member of the family or a relative has also had a severe reaction to an insect. In both instances, they had not been advised to seek further treatment. It had been lightly passed off by the doctor and the patient.

One physician at a state medical meeting at which I spoke told me that he had signed the death certificate of a person who had been plowing. He was heard to yell, "I've been stung" and fell over dead. He told me that the victim's wife had informed him that the man had had a previous reaction to an insect sting. The physician did not believe a person could die from an insect sting and had therefore signed the death certificate as due to heart attack.

I am appalled when I realize that an insect sting kit in the hands of any person allergic to insect stings could prevent sting-induced death. The time interval between an insect sting and death is around 10 to 20 minutes and usually is not enough time to get to a physician for life-saving treatment. I would like to see our legal statutes changed to allow any layman to purchase the insect sting kit over the counter at any drug store. If this is not feasible at least the kit should be available to emergency personnel — forest rangers, rescue squad personnel, school nurses, etc. Intensive education for the lay public, an absolute necessity, could begin with use of television and the printed media.

In the last few months I wrote a letter to the Editor to medical journals across the United States in which I asked physicians for their opinion on insect sting kits being made available to emergency personnel. State laws may vary but in most states if a child is suffering from a severe reaction as a result of an insect sting it is illegal for a school nurse to give him an injection of epinephrine to save his life. (The Journal of the Maine Medical Association may want to take some action to supporting the changing of this law.) I received many replies from physicians who wholeheartedly agreed that these people should have an insect sting kit on hand. To my dismay, without exception, *no physician* who replied knew of such a kit, its contents, and indications for use. The concern and interest is there. The knowledge is not. Pharmacists, the Department of the Army, and the Public Health Service were among some of the large groups represented in the replies.

The letter bears out my urgent request for a concentrated world-wide education. Editorials and articles in all the medical journals (most all physicians see this type of patient), simply giving the symptoms or reactions, treatment by the physician, and proper medication for the patient to have on hand in case of another sting. Information about the insect sting kit, a medic alert emblem, and possibly of hyposensitization to these insects should also be included. Symposia and lectures at the local, state and national medical meetings would be of great benefit to physicians and knowledgeable physicians could be stimulated to educate the layman through the local and national media.

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Dermatitis Herpetiformis

A Multi-System Disease Confirmed With Scanning Electron Microscopy of the Jejunum

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INTRODUCTION

Dermatitis herpetiformis (Duhring-Brocq's Disease) is a bullous skin disorder of unknown etiology. It is characterized by intensely pruritic blisters of varying size which tend to occur on reddened urticarial areas of skin. These are distributed in a bilaterally symmetrical fashion on the shoulders, buttocks, knees, elbows and occasionally on other pressure points.¹ Though the skin lesions are the hallmark of this disease, the finding of immune complexes in the serum of these patients has suggested a more systemic nature of the disease.² Case reports of its occurrence with glomerulitis,³ autoimmune hemolytic anemia,⁴ pernicious anemia

and thyrotoxicosis⁵ have supported this view and suggested an underlying autoimmune process. Furthermore, many, if not most, of these patients have a small bowel lesion histologically similar to that of adult celiac sprue.⁶ However, unlike the skin lesion which usually responds to dapsone or sulfapyridine, resolution of the small bowel lesion requires corticosteroids or a gluten-free diet.⁷ The histocompatibility antigen HL-A-8 has been found in a high percentage of dermatitis herpetiformis cases in which the small bowel lesion has been present,⁶ suggesting some genetic factor is involved in the pathogenesis.

Observations in this disease made with the light and transmission electron microscope are reported in the literature.^{8,9}

Scanning electron microscopy allows for evaluation of the absorptive surface as it is influenced by nutrition. Studies on the influence of fasting in avian species have shown that epithelial degeneration is induced in the small intestine of the fasted animal and the resulting topographical changes are readily observed with the scanning electron microscope.¹⁰

The purpose of this report is to present our morphologic observations using the scanning electron microscope of the jejunal mucosa in a patient with dermatitis herpetiformis and malabsorption.

CASE REPORT

A 49-year-old man was admitted to the Veterans Administration hospital, Togus, Maine for evaluation of diarrhea of two months' duration. He described having three to four watery bowel movements daily occurring without cramps and containing no blood. These were distributed throughout the day and occasionally awakened him at night. At no time were they bulky

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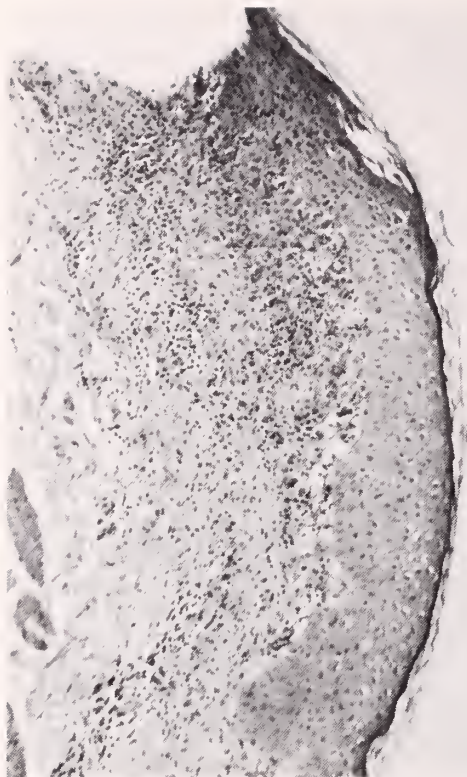


Fig. 1. Skin biopsy showing cleavage vesicle at epidermal-dermal junction. (H&E, x40)

or foul smelling. Though his appetite remained good he had lost 15 pounds in the previous year. Further, his weight was approximately 55 pounds below his normal weight.

The patient's past medical history was significant in that he had been diagnosed as having dermatitis herpetiformis 31 years previously. Over the years he had been troubled with typical blistering, intensely pruritic eruptions on the buttocks, scapulae, and extensor surfaces of the forearms. These generally had been responsive to sulfapyridine.

The family history was significant in that his grandmother had died of carcinoma of the esophagus and his mother had had chronic glossitis, pernicious anemia, and died of carcinoma of the colon.

Physical examination revealed a pale wasted white male with skin eruptions on the forearms, buttocks and scapulae. The primary lesion was a blister surrounded by an area of erythema. Secondary crusting of older lesions also was noted. There was no hepatosplenomegaly or lymphadenopathy.

METHODS AND MATERIALS

Small bowel biopsy was performed under fluoroscopy using the Quinton multipurpose section biopsy tube (Quinton Model 4.7 mm). The biopsy specimen averaged 2 mm in diameter and was divided equally for examination by light transmission and scanning electron microscopy. For light transmission microscopy, the tissue was fixed and embedded in paraffin by standard laboratory procedures. The embedded tissue was sectioned at 4 microns and further prepared for staining with hematoxylin and eosin (H&E). For scanning electron microscopy, the biopsy sample was fixed in 2% glutaraldehyde and Millonig's buffer, dehydrated in ethanol solutions, transferred to amyl acetate and critical point dehydrated using liquid CO₂ as the intermediary fluid. Dehydrated specimens were placed on aluminum stubs and 600 Å of gold-palladium (60:40 w/w) was vacuum evaporated onto the surface. Samples were examined with a Cambridge Stereoscan S-4 Scanning Electron Microscope.

RESULTS

Clinical laboratory findings revealed the following: Stool for

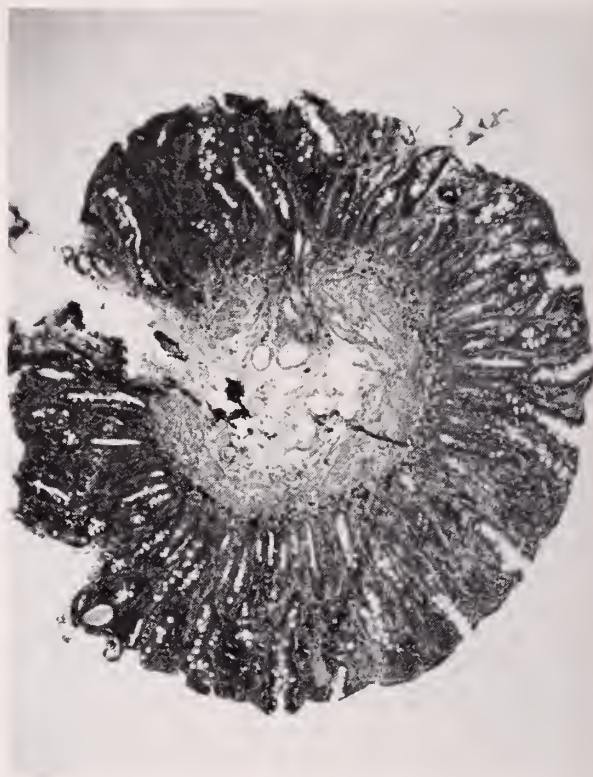


Fig. 2. Cross-section of jejunal mucosa showing loss of villi. (H&E, x40)



Fig. 3. Same specimen as in Fig. 2. (H&E, x100)

Sudan fat stain, 4+; serum calcium, 9.6 mg/dl; albumin, 2.94 gm/dl, globulin, 2.76 gm/dl; prothrombin time, 10.7/12.3; D-xylose tolerance, 3.8 gm urinary excretion (N=4-8 gm excreted); serum carotene, 50 mcg/ml (N=100-300); serum folate,

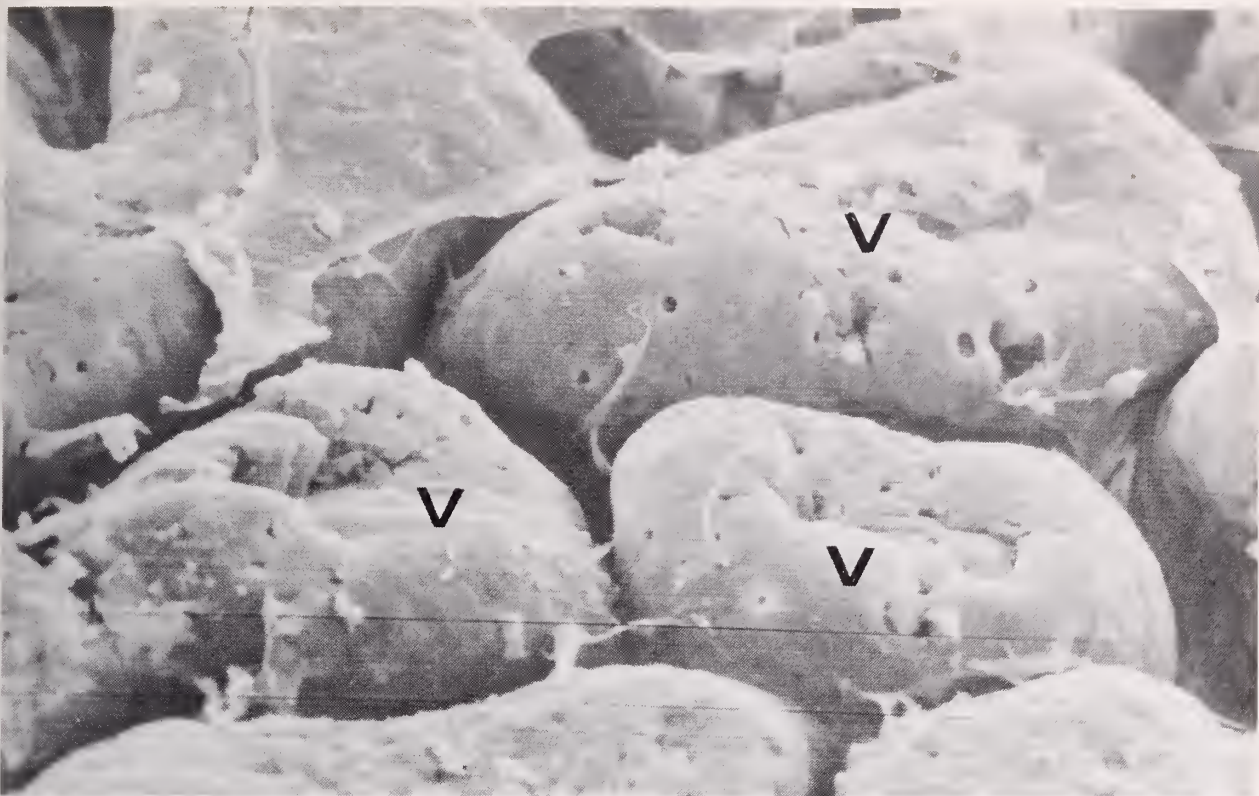


Fig. 4. Scanning electron micrograph of a portion of normal duodenum demonstrating normal appearing villi (V). (x450, 45°)

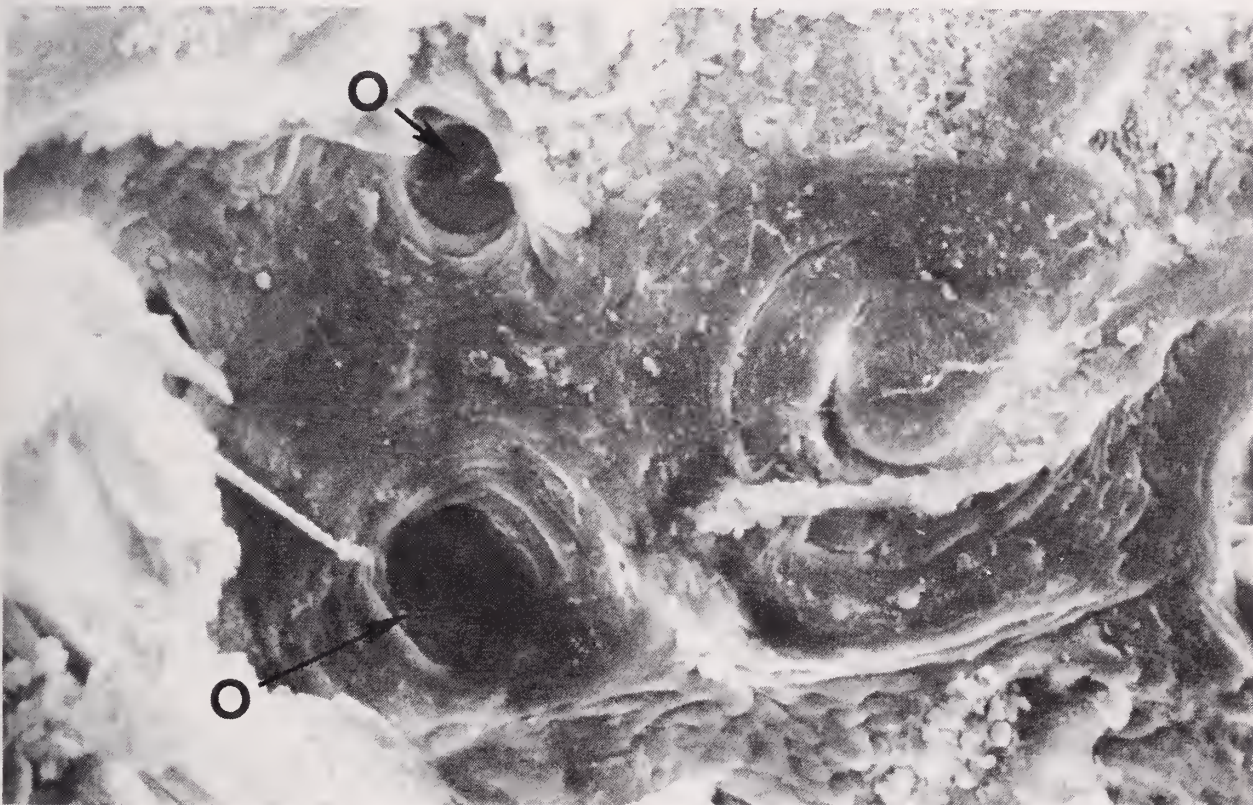


Fig. 5. Scanning electron micrograph of the mucosal surface of the jejunum from the patient with dermatitis herpetiformis. Villi are totally absent. The orifices (O) of the crypts are prominent. (x720, 56°)

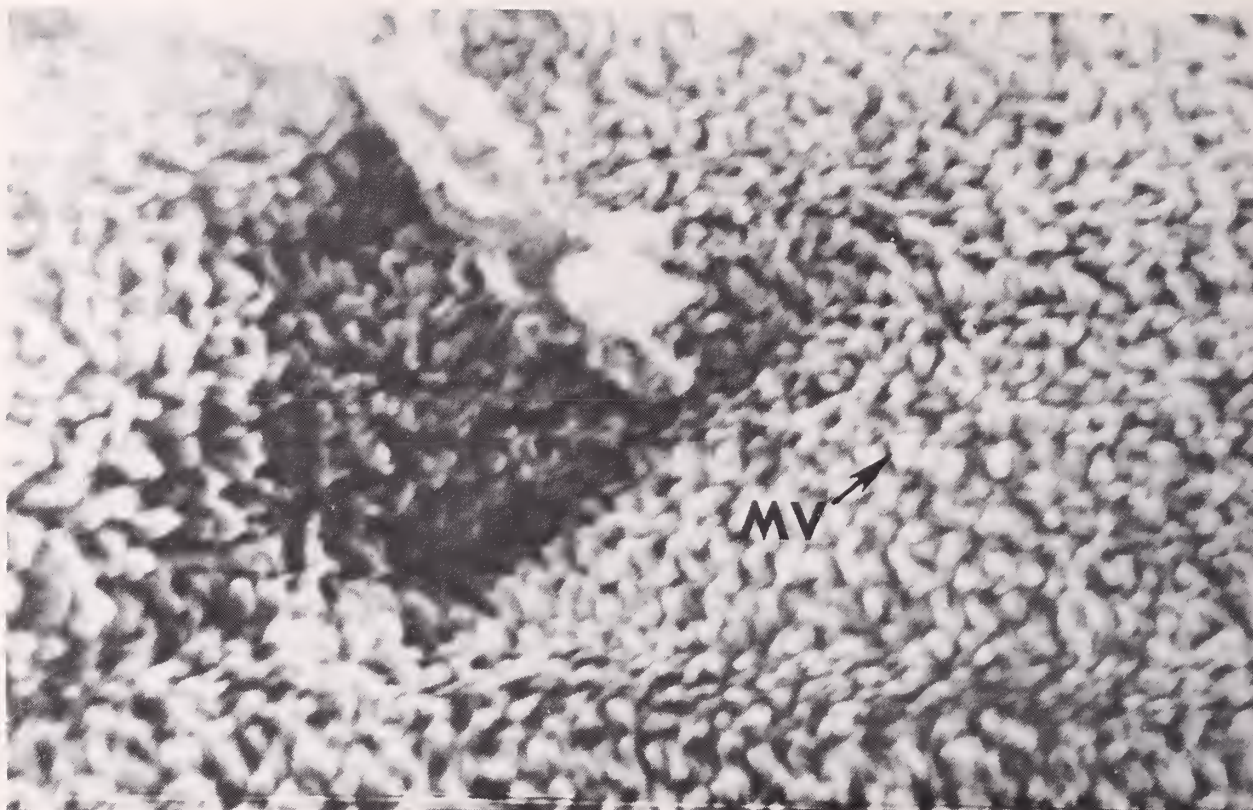


Fig. 6. Scanning electron micrograph of a portion of the mucosal surface of the jejunum from the patient with dermatitis herpetiformis showing apparently normal microvilli (MV). (x12,000, 56°)

2.2 ng/ml (N=4-16); B₁₂, 376 pg/ml; Schilling test, 18% excreted; gastric pH, 1.0; serum iron, 101 mcg/dl; total iron binding capacity, 275 mcg/dl; glucose tolerance test, fasting 91 mg/dl, 1-hr. 108 mg/dl, 2-hr. 92 mg/dl, 3-hr. 82 mg/dl; cholesterol, 140 mg/dl; hematocrit, 35% with the MCV 120, MCH 39, MCHC 31; the bone marrow showed megaloblastosis, and parenteral folate resulted in a reticulocytosis (9.2%).

A small bowel x-ray showed segmentation of the small bowel barium column and evidence of thickened mucosal folds.

HL-A typing of lymphocytes by Dr. Carpenter of the Peter Bent Brigham Hospital revealed HL-A 1 and 8.

A biopsy of the skin lesion showed a cleavage vesicle at the epidermal-dermal junction. There was a collection of neutrophilic and eosinophilic leucocytes within the vesicle and extending into the upper layer of the dermis (Fig. 1).

Hematoxylin and eosin stained microsections of jejunal mucosa obtained by the Quinton biopsy tube showed a circular piece of jejunal mucosa in which there was absence of all villi. The epithelium lining the crypts was normal. There was normal cellularity of the lamina propria (Fig. 2 and 3).

RESULTS OF SCANNING ELECTRON MICROSCOPY

The portion of biopsy material that was prepared for scanning electron microscopy graphically demonstrates the absence of villi as a topographical feature of the jejunum thus confirming the histological observation. Orifices, however, are readily apparent in this section (Fig. 5). At a greater magnification of the area (x12,000) apparently normal microvilli are revealed to adorn the jejunal surface (Fig. 6).

SUMMARY

A case report has been presented in which the clinical, laboratory and histological findings confirmed the presence of dermatitis herpetiformis and its manifestation as a multi-system disease entity. The scanning electron microscope has been

used in conjunction with light transmission microscopy of histologically prepared sections from the same biopsy material to confirm and better visualize the surface topographical characteristics induced in the small intestine by this disease. The apparent decrease in the total absorptive surface area due to lack of villi provides evidence of the malabsorption syndrome.

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Electrocardiographic Changes During Lithium Therapy

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ABSTRACT

Electrocardiographic changes were monitored during the first four weeks of treatment with lithium (38) or placebo (40) in 78 chronic alcoholic patients. The incidence of lowering and altered contours of the T waves was significantly higher among the lithium treated subjects. Only one electrocardiogram was reported as border line and none was interpreted as abnormal during the observation period. The previously reported view that electrocardiographic changes due to lithium are usually benign was supported.

INTRODUCTION

There has been a rapid increase in the experimental and clinical use of lithium as a psychotropic drug since Cade¹ reported his original findings in 1949. Such widespread use has quite naturally resulted in many reports of side effects. The effects of lithium on the heart and/or the electrocardiogram have been the subject of many of these reports. While most of the electrocardiographic changes attributed to lithium have been judged to be benign and reversible, there have been reports of major adverse cardiac effects.

The disastrous results from the use of lithium as a salt substitute are well known. Eleven cases of lithium intoxication were reported by Corcoran, et al² and Hanlon, et al³ from this use. There were three fatalities and in all of these arteriosclerotic heart disease had been diagnosed prior to treatment. Quite clearly lithium caused their deaths and from this came the firm conclusion that lithium should be given to patients with overt heart disease only with the greatest of caution. It should never be given to a patient requiring a low sodium intake.

In 1971, Tseng⁴ reported a fatal case of interstitial myocarditis which he attributed to lithium. Schou,⁵ in commenting on this case, expressed doubt that lithium caused the myocarditis and cautioned against over-concern for electrocardiographic deviations from the pre-treatment pattern.

The great majority of reports of electrocardiographic changes due to lithium over the past twenty years has been concerned with T waves. There have been no consistent reports of changes in P waves

and QRS complexes. Electrocardiographic changes simulating hypokalemia were reported in 1971 by Kochar,⁶ and potentially serious ventricular arrhythmia was reported by Tangedahl⁷ in 1972. In both of these instances normal serum potassium was found but intracellular potassium depletion was suspected. Return to pre-treatment electrocardiographic patterns resulted from stopping or lowering of the dose of lithium in both situations.

The reports of T wave changes with lithium treatment have consisted of depression and lowering for the most part and have been reported with increasing frequency. Most of these reports have been concerned with electrocardiograms which were normal before treatment. However, Schou,⁸ in 1962, reported a small group of patients with abnormal pre-treatment tracings which remained unchanged on treatment. By contrast, he found T wave depression and lowering in about 30% of patients with normal pre-treatment tracings. He considered these changes to be benign and reversible. Demers and Heninger^{9,10} in 1970 and 1971 in controlled studies found the incidence of such changes to be as high as 100%.

In a pilot study concerned with evaluating lithium as treatment for chronic alcoholism, electrocardiograms were monitored at infrequent intervals in a small number of patients.^{11,12} The finding of significant T wave lowering was about 30% and was consistent with other reports. In the present study, we have investigated electrocardiographic changes in a larger number of alcoholic patients on lithium and have compared them with a placebo group.

THE STUDY

Seventy-eight subjects for this study were obtained from a group of chronic alcoholic patients under investigation with lithium and placebo. All patients qualified as alcoholic under criteria set down in the Diagnostic and Statistical Manual of the American Psychiatric Association.¹³ The patients were all male with an age range of 30 to 55 — mean 46. Informed consent was obtained from the patients after the nature of the procedure had been fully explained.

All patients were inpatients when selected, having entered the hospital for detoxification. All had had routine physical and laboratory investigations with particular reference to cardiovascular, renal, and hepatic systems. Any with major deviations in these systems were excluded. Those who qualified were then assigned to a final preparation period. All drugs were stopped at this time.

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TABLE 1

PERCENTAGE OF LEADS WITH T WAVE LOWERING OF 1 MM OR MORE								
	Medication Period 1 2 days		Medication Period 2 7 days		Medication Period 3 14 days		Medication Period 4 28 days	
	PL	LI	PL	LI	PL	LI	PL	LI
Lead I	2.5	10.5	12.5	20.5	5.4	20.5	6.0	27.0
Lead II	10.0	10.5	12.5	18.0	A 5.4	A 37.0	A 12.1	A 51.3
Lead V-2	37.5	31.4	27.5	41.0	B 48.6	B 57.9	B 42.4	B 62.2
Lead V-3	37.5	34.2	35.0	51.3	56.7	71.0	60.6	63.2
Lead V-4	30.0	26.3	30.0	56.4	38.0	63.1	39.3	67.5
Lead V-5	17.5	34.2	C 17.5	C 43.3	C 32.4	C 71.0	C 18.0	C 75.6
Average serum lithium level		28.57 mEq/L		53.75 mEq/L	D	D 65.8 mEq/L	E	E 66.97 mEq/L

A — significant by Chi Square ($P > .05$)B — significant by Chi Square ($P > .01$)C — significant by Chi Square ($P > .05$)D — significant by Chi Square ($P > .01$)E — significant by Chi Square ($P > .001$)

PL = PLACEBO

LI = LITHIUM

During this period of ten to fifteen days, each patient had two base line electrocardiograms at a ten day interval. The electrocardiograms for the study were all done by the same technician and with the same instrument. The tracings were all standard 12 lead electrocardiograms using an instrument with a paper speed of 25 mm/sec. and a sensitivity of 1 cm/mv. Precordial leads were placed over marked areas to insure maximum uniformity.

At the end of the final preparation period, the patients were assigned at random to lithium (38) or placebo (40) groups. They were then started on lithium or identical placebo beginning with 600mg daily, increasing to 900mg daily after two days and continuing a dose of 900mg to 1500mg daily in divided doses depending on serum lithium levels. The objective was to attain and maintain a level between 0.6 mEq/L and 1.0 mEq/L. Placebo patients were given a similar number of tablets in order to maintain blind conditions for all except the one physician prescribing medication (JCW). The patients remained in the hospital for the initial medication period of four weeks. For purposes of this study, each patient had an electrocardiogram and serum lithium determination after 2 days, 7 days, 14 days and 28 days of medication.

No other drugs were used throughout the final preparation period or during the four-week period after investigative medication was started. There was no control on diet. The patients ate a standard hospital diet for ambulatory patients. There could be no absolute assurance that there was no alcohol intake. All standard laboratory studies were repeated at the end of four weeks and there were no significant deviations from normal pre-treatment values.

All electrocardiograms were interpreted under blind conditions by one of us (JBD). All base line tracings were interpreted to be within normal limits. Subsequent tracings on medication were interpreted with particular reference to the height of T

TABLE 2

PERCENTAGE OF T WAVES LOWERED MORE THAN 1 MM				
	LIMB		PRECORDIAL	
PLACEBO	17 of 906	1.87%	163 of 906	18%
LITHIUM	70 of 910	7.7%	315 of 910	34.6%
	$P > .001$		$P > .001$	

waves (from base line to peak) compared to the average height of T's in the two base line tracings. In addition, T waves were carefully scrutinized for alterations of contour. The results to be reported involved the examination and measurement of T waves in well over 5,000 leads.

RESULTS

The average height of the T waves for each lead of the two base line tracings was first determined. Variation of 1 mm or more between the base tracings was then noted as a measure of well known spontaneous variation in electrocardiograms. Any variation in T wave heights of less than 1 mm was not considered significant for the purpose of this study. As expected, in a substantial percentage of leads the T waves varied 1 mm or more in height. In the precordial leads of the base line tracings up to 57% of T waves varied 1 mm or more between tracings, while in the limb leads this variation was in the range of 18%.

After medication with placebo or lithium, T waves were measured at intervals of 2, 7, 14 and 28 days. The percentage of T waves lower by 1 mm or more than the average in the base line tracings was determined. We then compared the incidence of T wave lowering in those medicated with placebo to that in those medicated with lithium.

Thirty-seven patients were observed on lithium for a full four weeks. In 27 of these, there was significant lowering of the T waves in one or more limb leads at some time during the observation period. Similar findings were demonstrated in one

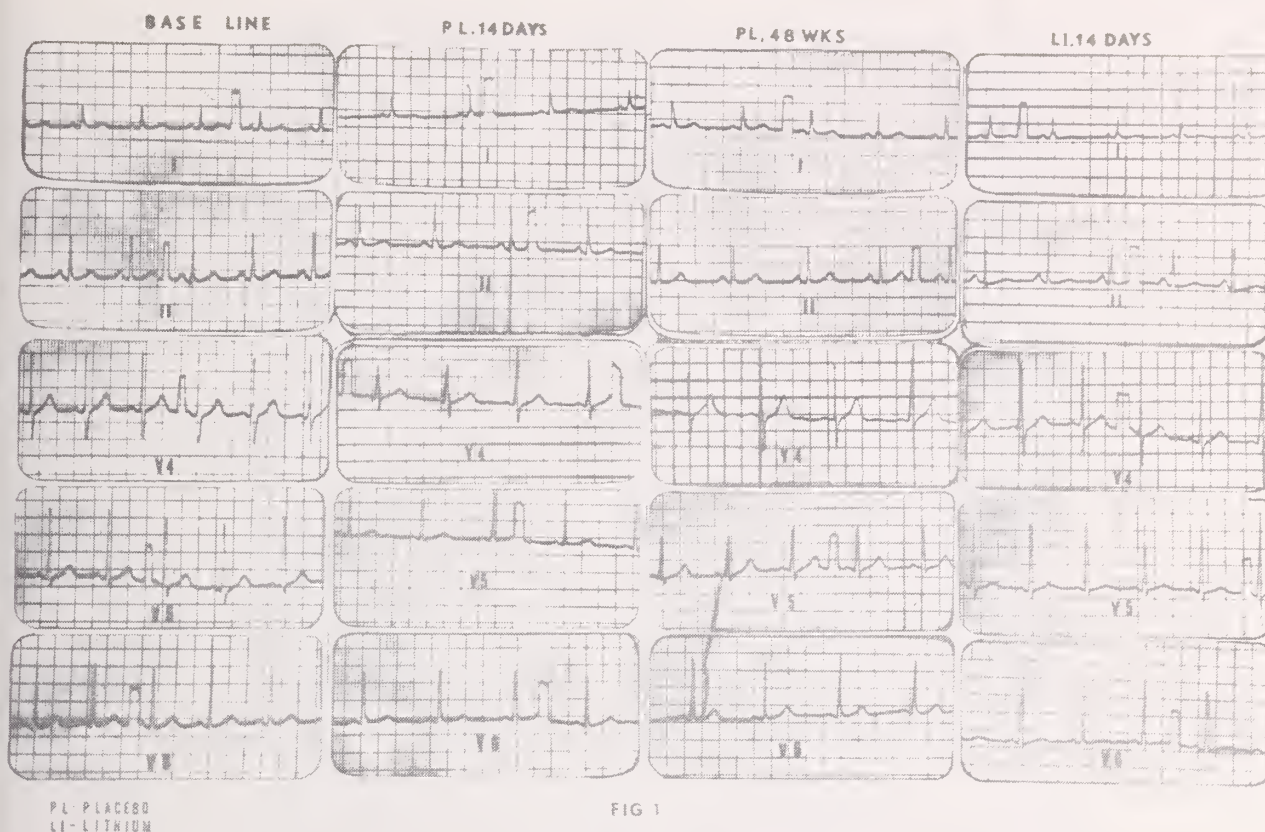


FIG 1

Fig. 1. This case illustrates significant lowering of T waves after 14 days with both placebo and lithium.

or more precordial leads of all 37 of these patients. Of thirty-three patients observed for four weeks on placebo, 17 showed noteworthy T wave lowering at some time in the limb leads, while 31 had similar findings in the precordial leads.

In order to assess the significance of the difference in evidence of T wave lowering between placebo and lithium treated patients, leads I, II, V-2, V-3, V-4 and V-5 were selected as most representative. T wave lowering of 1 mm or more compared to base line was determined for each of these leads at intervals of 2, 7, 14 and 28 days after starting medication. Table 1 summarizes all of these data and includes mean serum lithium values at the four intervals indicated.

Overall, the percentage of T waves lowered 1 mm or more while on lithium was greater than placebo. In leads V-2, V-3 and V-4 after two days of treatment, the percentage lowered on placebo was greater. Of all other treatment periods in all leads, the percentage lowered under lithium treatment was greater. The statistical significance of this difference varied rather widely as noted in Table 1. Of particular interest is the fact that in only one instance (V-4) was the difference of statistical significance after seven days of treatment. In V-2 and V-3, the differences were not significant at any period of treatment while in the limb leads and V-4 and V-5 the differences were all significant after 14

and 28 days of treatment. The probability tests by Chi Square varied from $P > .05$ (lead I) to $P > .001$ (V-5).

Mean serum lithium levels for four periods of treatment are included in Table 1. It should be recalled that for this experiment the objective was to attain and maintain levels within the so-called prophylactic range. After seven days the mean was in the low part of this range and after 14 and 28 days, while the values were higher and remarkably similar, they remained in the lower portion of the prophylactic range. Despite this, the incidence of T wave changes was generally much higher at these treatment intervals, suggesting that duration of treatment had more influence on the electrocardiographic changes than serum levels as such.

We next considered the degree of T wave lowering for both groups. For the lithium treated patients, T waves in limb leads were sometimes lower by as much as 3.5 mm, while in the precordials the range was up to 5.5 mm. By contrast, these ranges were 1.25 mm and 2.75 mm respectively for the placebo patients.

Table 2 shows the number of T waves lowered by more than 1 mm for both groups. For this determination, all leads of all electrocardiograms done during treatment were considered. It is readily apparent that the degree of lowering of the T waves was significantly greater in the lithium group.

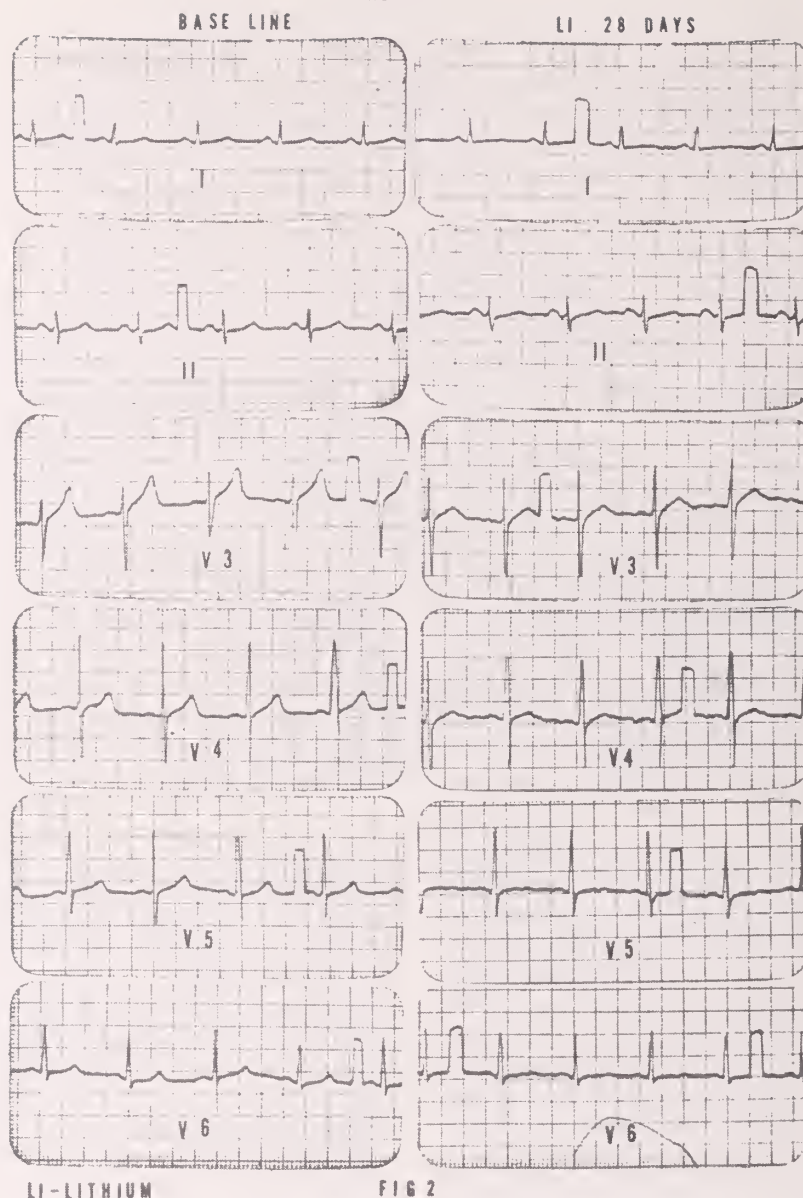


Fig. 2. There is in addition to significant lowering of T waves obvious notching of the T waves in the left precordial leads.

In addition to lowering of the T waves while on lithium, some significant changes in the contours of the T waves were noted. Some occasional variation in contours of T waves is well known to occur spontaneously but it is rather infrequent. In a little over half of the lithium group, significant changes in contours were observed when compared to base line. These changes consisted of rounding, flattening or plateau formation and notching. As previously noted, the tracings were interpreted under double blind conditions by one of us (JBD). It is of particular interest to emphasize the fact that in no case was an electrocardiogram interpreted as abnormal after treatment was begun and a border line interpretation was made in only one case (case 154, Fig. 2).

Figures 1, 2 and 3 illustrate T wave lowering which occurred both spontaneously and after treatment with lithium and also demonstrate rounding, flattening, plateau formation, and notching.

COMMENT

From these results, there seems to be little doubt but that lowering of T waves to a significant degree occurs during lithium treatment. Evidence is presented that the incidence of these changes is significantly greater than that observed spontaneously. The actual measurable lowering is significantly greater with lithium when compared to placebo. Contour changes at times are very obvious as illustrated in Figures 2 and 3.

Most previous investigators have suggested that

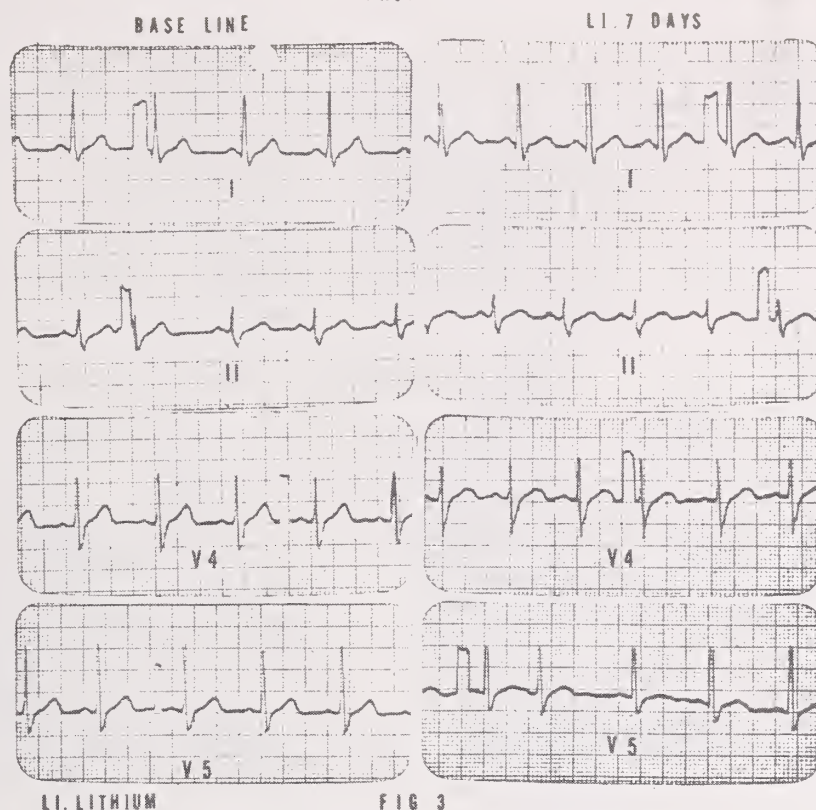


Fig. 3. T waves show both rounding and plateau formation after seven days of lithium treatment.

these findings are benign and reversible. It has been noted that despite the rather obvious changes from base line no tracings were interpreted as abnormal, and in only one case was a reading border line (case 154, Fig. 2). We therefore share the view that electrocardiographic changes due to lithium are most likely of a benign nature. It should be added that no patients showed any sign of cardiovascular malfunction during this study.

The mechanism of the development of electrocardiographic changes with lithium remains unknown. Further, our studies suggest that the changes are probably not related to the serum lithium level. In one previous study,¹⁰ it was suggested that electrocardiographic changes from lithium usually occurred within five days. In the present study, the incidence of changes was much higher after 14 and 28 days of treatment.

Intracellular accumulation of lithium may occur in the presence of relatively low serum levels. It is suggested that this may account for this difference.

ACKNOWLEDGMENTS

We wish to thank Mr. Richard A. Anderson, B.A., for doing the statistical analysis. We wish to thank Pfizer Pharmaceuticals for supplying the medication used in this study.

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Testing in Humans: Who, Where & When.

The weight of ethical opinion:

Few would disagree that the effectiveness and safety of any therapeutic agent or device must be determined through clinical research.

But now the *practice* of clinical research is under appraisal by Congress, the press and the general public. Who shall administer it? On whom are the products to be tested? Under what circumstances? And how shall results be evaluated and utilized?

The Pharmaceutical Manufacturers Association represents firms that are significantly engaged in the discovery and development of new medicines, medical devices and diagnostic products. Clinical research is essential to their efforts. Consequently, PMA formulated positions which it submitted on July 11, 1975, to the Subcommittee on Health of the Senate Labor and Public Welfare Committee, as its official policy recommendations. Here are the essentials of PMA's current thinking in this vital area.

1. PMA supports the mandate and mission of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research and offers to establish a special committee composed of experts of appropriate disciplines familiar with the industry's research methodology to volunteer its service to the Commission.

2. PMA supports the formation of an independent, expert, broadly based and representative panel to assess the current state of drug innovation and the impact upon it of existing laws, regulations and procedures.

3. When FDA proposes regulations, it should prepare and publish in the *Federal Register* a detailed statement assessing the impact of those regulations on drug and device innovation.

4. PMA proposes that an appropriately qualified medical organization be encouraged to undertake a comprehensive study of the optimum roles and responsibilities of the sponsor and physician when company-sponsored clinical research is performed by independent clinical investigators.

5. PMA recognizes that the physician-investigator has, and should have, the ultimate responsibility for deciding the substance and form of the informed consent to be obtained. However, PMA recommends that the sponsor of the experiment aid the investigator in discharging this important responsibility by providing (1) a document detailing the investigator's responsibilities under FDA regulations with regard to patient consent, and (2) a written description of the relevant facts about the investigational item to be studied, in comprehensible lay language.

6. In the case of children, the sponsor must require that informed consent be obtained from a legally appropriate representative of the participant. Voluntary consent of an older child, who may be capable of understanding, in addition to that of a parent, guardian or other legally responsible person, is advisable. Safety of the drug or device shall have been assessed in adult populations prior to use in children.

7. PMA endorses the general principle that, in the case of the mentally infirm, consent should be sought from both an understanding subject and from a parent or guardian, or in their absence, another legally responsible person.

8. Pharmaceutical manufacturers sponsoring investigations in prisons must take all reasonable care to assure that the facilities and personnel used in the conduct of the investigations are suitable for the protection of participants, and for the avoidance of coercion, with a respect for basic humanitarian principles.

9. Sponsors intending to conduct non-therapeutic clinical trials through the participation of employee volunteers should expand the membership and scope of its existing Medical Research Committee, or establish such an internal Medical Research Committee, with responsibility to approve the consent forms of all volunteers, designs, protocols and the scope of the trial. The Committee should also bear responsibility to ensure full compliance with all procedures intended to protect employee volunteers' rights.

10. Where the sponsor obtains medical information or data on individuals, it shall be accorded the same confidential

status as provided in codes of ethics governing health care professionals.

11. PMA and its member firms accept responsibility to aid and encourage appropriate follow-up of human subjects who have received investigational products that cause latent toxicity in animals or, during their use in clinical investigation, are found to cause unexpected and serious adverse effects.

12. PMA supports the exploration and development by its member companies of more systematic surveillance procedures for newly marketed products.

13. When a pharmaceutical manufacturer concludes, on the basis of early clinical trials of a basic new agent, that a new drug application is likely to be submitted, a proposed development plan accompanied by a summary of existing data, would be submitted to the FDA. Following a review of this submission, the FDA, and its Advisory Committee where appropriate, would meet with the sponsor to discuss the development plan. No *formal* FDA approval should be required at this stage. Rather, the emphasis should be on identification of potential problems and questions for the sponsor's further study and resolution as the program develops.

The PMA believes that health professionals as well as the public at large should be made aware of these 13 points in its Policy on Clinical Research. For these recommendations envisage constructive, cooperative action by industry, research institutions, the health professions and government to encourage creative and workable responses to issues involved in the clinical investigation of new products.



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Villous Adenoma of the Rectum Associated With Severe Electrolyte Imbalance

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Frequent bowel movements associated with the excretion of large amounts of watery mucus is an infrequent but striking symptom of villous adenoma of the large intestine. In some patients with this entity, fluid and electrolyte loss is sufficient to result in severe electrolyte imbalance characterized by hyponatremia, hypokalemia, hypochloremia, metabolic alkalosis and prerenal azotemia. The following case report illustrates dramatically some of the problems in the preoperative and operative management of such a patient.

CASE REPORT

H. T., a 53-year-old male, was admitted to the hospital on March 16, 1976 with a three-year history of frequent watery stools associated with large amounts of mucus. After symptoms of approximately one year, he had seen his physician who following the performance of a proctoscopy and barium enema had advised surgical treatment. This advice was rejected and the patient made the decision to have nothing done and defer surgical management until it became absolutely mandatory. Thereafter, despite frequent bowel movements and slowly progressive weakness, the patient remained at work until approximately two and a half weeks prior to this present admission. At that point he developed what he believed was an upper respiratory tract infection which was associated with anorexia, nausea, vomiting and frequent diarrheal stools. Because of this illness resulting in effect in a severe exacerbation of his prior intestinal symptoms, there was severe weakness, dizziness and confinement to bed.

On examination he was found to be weak, lethargic and mentally obtunded. His temperature was 95° F., pulse 88, respirations 18 and blood pressure 76/64. The tongue and pharynx were dry and the skin and subcutaneous tissue was dry, loose and inelastic. His abdomen was flat, soft and without masses or tenderness. Digital rectal examination revealed the ampulla to be free of feces and no masses were palpable. A chest roentgenogram was negative and flat films of the abdomen showed the large intestine to be full of feces but there was no evidence of obstruction. Laboratory studies done at this time revealed the following: Urinalysis showed a specific gravity of 1.014, pH 5.0, with 2-3 red blood cells, and 2-3 white blood cells per high powered field as well as occasional granular cast per slide. Blood studies showed hemoconcentration and leukocytosis and the chemical studies showed elevation of the BUN and creatinine with severe derangement of the electrolyte values (Table 1). A barium enema carried out the day after admission confirmed the presence of a huge intrarectal tumor. Proctoscopy performed several days after admission revealed a large, soft, sessile villous tumor involving almost the entire length of the rectum and completely encircling the lumen. Intestinal mucus was present in copious amounts. There was no ulceration, no firm neoplastic mass, and all biopsies were negative for cancer.

Because of the severity of the volume depletion, low urine output and azotemia, hydration and electrolyte replacement were considered of primary importance. This was done cautiously at first and later normal saline, potassium chlorides and hypertonic saline were administered by central venous catheter (Table 2). In two days, approximately 900 mEq of sodium chloride were administered in each twenty-four hour period. On other days, from 350 to 450 mEq were given each day. Potassium chloride was also administered daily at the rate of from 200 to 300 mEq per day. During the entire period he also received fluids by mouth of from 1300 to 3700 ml per day.

By the 6th and 7th hospital day, a normal state of hydration had been reached and serum electrolyte values had become relatively normal. It was now felt that the patient had at last reached an optimum condition for surgical management.

At operation it was found that an anterior resection of the rectum with an intrapelvic-colorectal anastomosis was not feasible because of the enormous size of the lesion. Only 4 to 5 cm of normal rectal mucosa was found present distal to the lesion and this was felt to be insufficient to allow a safe anastomosis with a functionally competent internal rectal sphincter. Accordingly, abdominoperineal resection was carried out. Recovery from this operation was rapid and the postoperative convalescence was free of complications.

Study of the pathological specimen revealed a huge, soft sessile lesion 19 cm in length and completely encircling the lumen (Fig. 1). It extended from above the peritoneal reflection to within 4 to 5 cm of the mucocutaneous junction. The small white arrow points out a small segment of tumor remaining at the level where an attempt was made to carry out complete removal from above and still effect an intestinal anastomosis. Microscopic examination revealed numerous finger-like projections covered with a single layer of columnar epithelium showing marked proliferation of cells with crowding, loss of polarity, and with normal appearing mitoses (Fig. 2 and 3). Much of the tissue appeared to be non-secretory but there were many focal areas where goblet cells predominated. There were no malignant changes.

DISCUSSION

Villous tumors of the large bowel are not frequently seen in hospital practice and represent from 2 to 5% of all benign and malignant colon tumors.^{1,2} They are also rarely found in other portions of the gastrointestinal tract such as the stomach and duodenum. Three to four percent of the tumors described in the literature are large ones such as the one observed in this instance. Bleeding is a major symptom in from 50 to 75% of the cases, diarrhea in from 25 to 50%, profuse mucus in the stool in from 12 to 30% and protrusion of tumor mass from the anus in from 10 to 20%. The average patient is somewhat older (65 years of age) than the average patient with large bowel cancer. In addition, the average patient with villous adenoma has had symptoms for a longer period of time (up to 15 years) in some instances. Eight to 100 percent are said to be or to become malignant depending upon the criteria used by the pathologist.^{2,3,4} If atypia

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TABLE 1

SIGNIFICANT PRE- AND POSTOPERATIVE LABORATORY VALUES

Date	BUN mg %	Creat. mg %	Na	K mEq/l	Cl mEq/l	CO ₂	Ca mg %	Prot. Gm %	A/G	Hct.	Hgb.	WBC	mosm
Serum Studies													
3/16	90		122	2.5	64	32	10.1	(Arterial pH — 7.464)					
3/17	129	4.7	120	2.6	60	25	9.7	9.5	4.6/4.9	57	18.8	26,600	276
3/18	142	3.8	116	2.6	73	25	8.0	6.8	4.0/2.8				337
3/19	93	1.9	131	2.6	99	19	7.2	5.1	2.7/2.4				
3/20	42	1.2	130	3.0	110	13				40	11.1	16,063	
3/21	16		138	3.8	106	20				34.5	11.8	13,760	
3/22	13	1.1	131	4.4	107	20	8.4	6.2	4.1/2.1	36	10.4	4,500	292
3/27			136	4.5	106	19				36	11.9		
4/7	19	0.9	133	3.7	98	34		6.7	3.6/3.1	36	11.7		
5/4	14	0.9	137	4.0	103	24							
Urine Studies													
3/17			6	30	3								350
3/19			36	12	28								
3/22													631
Rectal mucus													
3/24			109	17.6	89								

(Blood transfusions given on 3/24, 3/25 and 3/26)

TABLE 2

PREOPERATIVE FLUID BALANCES

Date	Oral	Intake			Output		
		I-V	Fluid	KCl	Urine	Stool	Weight
3/16	—	1000	N/S	30	—	++++ Mucus	143.0
3/17	1340	3000	N/S	130	725	++++ Mucus	
3/18	3730	6075	5% D/S (5% Sal. 500 cc)	300	3700	++++ 445	142.2
3/19	2220	6050	5% D/S	300	5100	2140	146.3
3/20	2820	4000	Alt. 5% D/W 5% D/S	200	3200	2675	149.8
3/21	2000	5850	"	300	1900	7620	148.3
3/22	1790	4900	"	250	700	5070	140.8
3/23	1500	5150	"	250	1340	2880	142.2
3/24	2310	4150	"	200	1590	3800	143.7
3/25	2160	2600	"	150	1000	5875	142.9

and carcinoma in situ are stressed, the higher figure may be given. If invasion of the muscularis mucosa is necessary for such a diagnosis, then from 8 to 20% would be the more probable incidence of malignancy. Lymph node involvement and liver metastases are reported occasionally.

What really sets the tumors apart from other large bowel tumors, benign or malignant, however, is the infrequent but striking association of severe and frequent passage of large amounts of electrolyte-rich mucus from the rectum. Incontinence is often a problem and severe electrolyte imbalance due to losses of large quantities of sodium, potassium and chlorides will develop occasionally.

The mechanism of development of copious mucoid, secretory diarrhea in this condition is not well understood. It has been noted, however, that these tumors are associated with secretory diarrhea with excessive secretion of sodium, chloride, potassium and water.^{5,6}

Some intestinal tumors have been found to secrete large amounts of prostaglandins which can cause secretion of water and electrolytes especially from jejunum.⁷

The watery diarrhea of the "watery diarrhea hyponatremic alkalosis syndrome" (WDHA Syndrome) ("Pancreatic cholera") has been found to be associated with very high levels of vasoactive intestinal peptides.⁸ Whatever the mechanism may be, the resultant biochemical changes are often dramatic and can lead to catastrophes if not recognized and treated promptly.

The presentation of vomiting with diarrhea in our patient at the time of admission raises the possibility of associated infection, although stool cultures were negative for bacterial or other pathogens. This in turn might have further decreased the absorption of water and electrolytes from the gut along with the loss of hydrogen and chloride with water through vomiting. The normal colonic con-

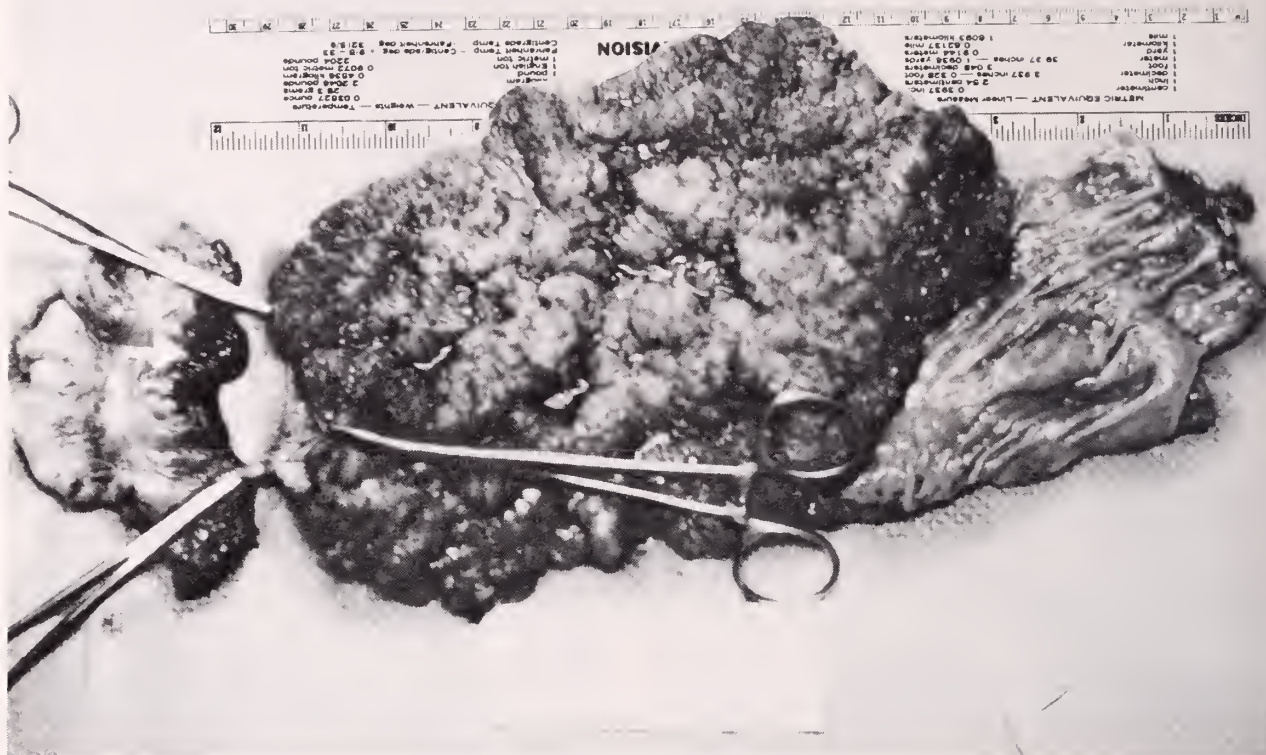


Fig. 1. Rectal tumor juxtaposed with 30 cm. ruler.

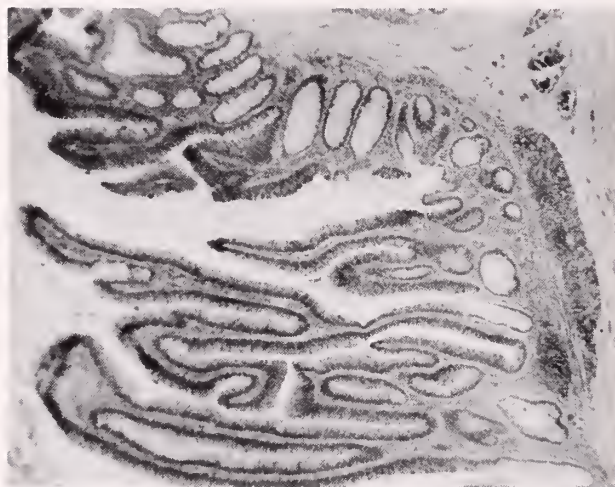


Fig. 2. Junction of normal colonic mucosa and villous adenoma. (x40)

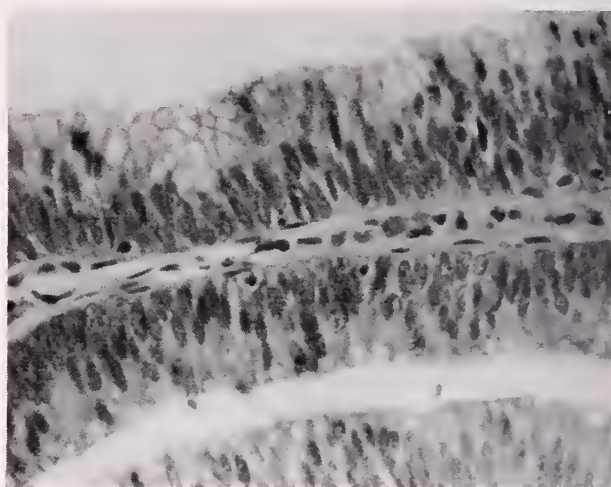


Fig. 3. Cellular detail of benign villous adenoma. (x450)

tent of electrolytes is stable with sodium, 25-50 mM; chloride, 15 mM; potassium, 80-130 mM and bicarbonate, 30 mM.⁶ The net flow and excretion of water and electrolytes in normal adults per 24 hours averages as follows: Water, 100-150 ml; sodium, 5 mM; potassium, 3-15 mM; chloride, 3 mM and bicarbonate, about 3 mM.⁶

The huge amount of sodium and chloride losses in the diarrheal fluid with water loss and losses of

hydrogen, chloride and water in vomiting resulted in volume depletion, hyponatremia and hypochloremia. This resulted in increased avidity for sodium reabsorption by proximal tubules. Reduced chloride concentration in the glomerular filtrate helped generate more bicarbonate in the proximal tubule to be reabsorbed as the anion to go with sodium, a phenomenon of increased threshold of bicarbonate reabsorption ($\uparrow TmHCO_3^-$).

The low urinary sodium and chloride in this case reflects depletion of extracellular volume, while high urinary potassium in excess of 30 mEq/day in the presence of hypokalemia is usually taken as primary renal potassium wastage. The extracellular fluid compartment (ECF) contraction also activates renin-angiotensin-aldosterone mechanisms thereby enhancing urinary potassium losses. In our patient, the combination of decreased dietary intake of potassium coupled with losses of the ion in the urine and to some degree in the stool resulted in marked hypokalemia and probably marked decrease in intracellular potassium stores. The reduction in renal tubular potassium stores is thought to favor hydrogen ion secretion and therefore to augment acid excretion and bicarbonate reabsorption.⁹ However, some recent studies have indicated that it is the chloride depletion which accounts for persistence of metabolic alkalosis and an elevation of the tubular bicarbonate reabsorption threshold.¹⁰ Acceleration of hydrogen and potassium ion secretion in the distal renal tubule due to a persistent demand for sodium reabsorption will result in "Paradoxical Aciduria" and maintenance of alkalosis.¹¹

The shift of sodium from the extracellular to the intracellular position helps to further decrease the serum sodium level. The activation of antidiuretic hormone due to marked volume depletion further aggravates existing hyponatremia by reducing free water clearance. All these factors mentioned above would also cause, as in our case, decrease in glomerular filtration and increased reabsorption of urea causing marked prerenal azotemia.

Correction of hyponatremia as rapidly as permissible to a level of greater than 120 mEq/l when the serum sodium is below this and especially if associated with neurological changes common to very low levels of serum sodium is very important and under careful monitoring use of hypertonic saline is recommended. The extracellular fluid depletion and metabolic alkalosis in this situation is best treated by use of normal saline.^{11,12,13} The concomitant potassium deficit is treated by potassium chloride with the saline under careful monitoring, especially if the patient has shown cardiac arrhythmias or if he is on a digitalis preparation.

Whereas the passage of mucus has long been found to be characteristic of this type of large bowel lesion, its relationship to electrolyte imbalance was not stressed in the surgical literature until 1954.¹⁴ In more recent years, a number of dramatic examples have been reported.^{15,16,17,18,19} Additional cases have also been mentioned in the discussion of other papers and new cases are now being reported every one or two years.

CONCLUSION

Severe volume depletion, electrolyte imbalance and prerenal azotemia, although a well-known entity, remains a somewhat rare physiological development in the patient with villous adenoma. It is a potentially lethal condition and it requires aggressive fluid and electrolyte therapy together with careful monitoring of intake and output electrolyte values, the electrocardiogram, and other parameters in order to assure a satisfactory outcome.

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The *Listeria Monocytogenes* Infection

A Case Report and Review of the Literature With Special Reference to the Cases in Maine

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Listeria monocytogenes, also called the "Cinderella of Bacterium," is a widely distributed gram positive rod which causes sporadic human infections.¹ The organism was first isolated by Murray in 1926 from a group of laboratory rabbits with a disease characterized by mononuclear cell leucocytosis and hence named *Bacterium monocytogenes*. In 1940, Pirie proposed the generic name *Listeria* and that became the official name. The organism has been mistaken often for diphtheroids, streptococcus, enterococcus, and even *Lactobacillus*.²

Since this disease is reportable on a voluntary basis, this fact coupled with the occasional difficulty in recognition of the bacteria results in only sporadic reports and the true incidence of the disease is not known. In the past 10 years, however, the disease has been recognized with increasing frequency.

The first reported case of Listeriosis in Maine was in 1958 in an infant who died of meningitis. Not all the tests required for identification of the bacteria were carried out, yet it appears that that was most probably the organism involved.

The purpose of this paper is to report a case of *Listeria* meningitis in an elderly man and review the literature with particular reference to the cases from the State of Maine.

CASE REPORT

A 58-year-old golf course attendant was admitted to the Veterans Administration hospital at Togus on Dec. 3, 1975 because of a fever of 103° F. and confused state of two days' duration. One week prior to admission the patient had noted "cold symptoms" with cough, sneezing, and scanty whitish sputum. On the day of admission, the patient became lethargic and the temperature rose to 103° F. There was no history of headache, chest pain, hemoptysis or head injury. There was no history of cancer, diabetes, or tuberculosis.

The past history included a cholecystectomy in 1965 and mild hypertension which was controlled with Reserpine. The patient was a heavy ethanol drinker, sometimes consuming up to one pint per day.

The blood pressure was 190/68, the pulse was 108 per minute. The temperature was 103° F. The patient appeared older than his age, was obese and lethargic. The neck was stiff on passive flexion. The fundi couldn't be well visualized as the patient constantly moved his eyes and head. The breath sounds were decreased and rhonchi and rales were present in the right lower scapular area. The heart was not enlarged. The heart sounds were normal without murmur or gallops. The abdomen was soft and without ascites. The liver was 16 cm. in span and was smooth and non-tender. The rectal examination was negative. The neurological examination revealed the patient to be lethargic,

responding poorly to verbal orders. The muscle tone was decreased all over with hyporeactive deep tendon reflexes. The plantar reflexes could not be obtained. The Kernig and Brudzinski signs were present. Further detailed neurological examination was not possible. There were no skin rashes except for a few spider angiomas over the chest. No lymphadenopathy was noted.

Laboratory studies on admission revealed the following values: White blood cell count (WBC) 10,867, with 79% neutrophils, 20% lymphocytes, and 1% monocytes; hematocrit, 51%; glucose, 160 mg/dl; sodium, 131 mEq/L; potassium, 3.5 mEq/L; chlorides, 100 mEq/L, and total CO₂ was 25 mEq/L. A 2-hour post-prandial sugar was 130 mg/dl. The SGOT was 15 mU/ml; LDH; 151 mU/ml; uric acid, 7.1 mg/dl; alkaline phosphatase, 1.7U/ml; total protein, 7.6 gm/dl; albumin, 3.6 gm/dl.

An x-ray of the chest showed basilar pneumonia.

The spinal fluid pressure was 280 mm of water. The fluid was turbid green with 200 cells/ml of which 70% were neutrophils and the rest lymphocytes. The spinal fluid glucose was 50 mg/dl and the protein 178 mg/dl. A gram stain of the fluid showed gram positive cocci and coccobacilli, some in pairs, with many polymorphonuclear leucocytes. The sputum gram stain showed polymorphonuclear leucocytes, gram positive cocci and gram negative bacilli. A culture of the spinal fluid grew *Listeria monocytogenes* which were confirmed by the biochemical and motility tests. The sputum culture grew *Klebsiella* and a few colonies of *Staphylococcus aureus*, coagulase positive. The urine and blood cultures did not grow any bacteria.

The patient was treated with 20 million units of penicillin per day for one month. He became afebrile on the second hospital day with an improvement in the neurological picture. A repeat spinal tap on January 12, 1976 showed the fluid had normal pressure, glucose was 70 mg/dl and the protein was 69 mg/dl. There were 3 to 4 polymorphonuclear leucocytes and a culture of the fluid was negative. A sputum culture at this time was negative as was an x-ray of the chest which was reported to be within normal limits.

The patient was discharged on January 14, 1976, completely recovered.

COMMENTS

Human infections with Listeriosis have been reported with increasing frequency although whether this is an increased incidence or an increased awareness of the physician and bacteriologist is a question. Table 1 shows the clinical features of Listeriosis in general and Table 2 shows a summary of clinical findings from cases reported in Maine from 1959 to the present case report.

EPIDEMIOLOGY

The true incidence of Listeriosis is probably not certain due to the lack of compulsory reporting. However, some large institutions have reported a mean yearly incidence as follows: Memorial Hospital of New York, 1.5 (7); Mount Sinai Hospital of New York, 2.5 (4); Massachusetts General Hospital, 2.4 (6); and Los Angeles County Hospital, 2.5 (5).

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TABLE 1

CLINICAL FEATURES OF LISTERIOSIS IN GENERAL 3,4,5,6	
A.	Fever, 90%
B.	Meningitis, 75%
C.	In varying orders, the following have been reported
1.	Septicemia
2.	Pneumonitis
3.	Endocarditis
4.	Conjunctivitis
5.	Cholecystitis
6.	Urethritis
7.	Vaginal infection
8.	Amnionitis
9.	Abortion and stillbirth
10.	Headache, confusion, seizure
11.	Skin lesion, papular eruption and/or ulcer with nonspecific distribution

some other case reports raises several questions including if, like immunosuppression (*Vide infra*), this illness also predisposes the vulnerable people at high risk of acquiring this ubiquitous bacterium with severe systemic manifestations.

Fecal carrier rates of *L. monocytogenes* have been found to range from 1 percent in a random population to 26 percent in household contacts of patients with Listeriosis,¹² although the same survey failed to isolate *Listeria* from stools of hospital contacts and thus makes the high carrier rate unlikely.

By far, most of the cases of Listeriosis have been either in newborn infants or the elderly. The remainder of the patients who presently form a major-

TABLE 2

CASES OF LISTERIOSIS IN MAINE					
Case No.	Sex	Age	Clinical Presentation	Outcome	Comment
1	M	3 weeks	Meningitis	Died	Probably first case report, lacked confirmatory biochemical identification
2	M	17 days	Meningitis	Died	
3	M	62 years	URI, ulcer over heels	Recovered	
4	M	30 years	Fever, acute tonsillitis	Improved	Mongol
5	M	37 years	Pneumonia	Died	Had completed anti-Tbc treatment 3 weeks prior to this episode
6	M	19 years	Bronchopneumonia	Recovered	Hospitalized for cerebral palsy
7	M	N-I*	Acute tonsillitis	N-I*	N-I*
8	M	20 years	URI	N-I*	N-I*
9	F	17 years	Septicemia, meningitis	Recovered, has residual Weber's Syndrome	Patient a renal transplant recipient, was on immunosuppression and hemodialysis
10	M	2 weeks	Meningitis	Recovered	
11	M	68 years	Pneumonia, meningitis	Recovered	Alcoholism, probable cirrhosis of liver

*N-I = No information available

The source of, or mechanism of spread of, infection is largely unknown as was true in our case. Rarely is it obvious as in one case of a veterinarian who developed cutaneous Listeriosis while attending a newborn calf.⁹ The *Listeria* were isolated from both the skin lesion and the calf.

Thirty-five mammals and 17 fowls including domesticated animals, zoo animals, and laboratory animals have been found to harbor *Listeria*.¹ The most frequent animal harboring *Listeria* is the chicken and the poultry workers seem to have a higher incidence of ocular lesions.¹⁰ Milk and silage also have been found to have *Listeria* and a history of ingestion of unpasteurized milk has been obtained in some cases of Listeriosis in rural children.

The mode of transmission in most cases is not clear. Person-to-person transmission has been implicated but in an outbreak in a nursery ward neither the staff members nor the mothers were found to have *Listeria*.¹¹ Similar findings appear to be the case in a recent outbreak in one South Carolina hospital where a cluster of 7 cases were reported in the nursery ward. The transmission mode has remained obscure.¹⁴

The role of a flu-like illness prior to the development of *Listeria* meningitis in our patient and in

ity are those who have been subjected to immunosuppression, treated with steroids, or have received radiation and/or had debilitating diseases including chronic alcoholism.^{3,4,5,6,7,15} The disease is present in a high number of cases of renal transplant recipients, patients with Hodgkin's disease and various other malignancies and tuberculosis. The preponderance and severity of the disease in this group of patients is probably related to a decreased cellular immunity due to either abnormal or decreased populations of T-lymphocytes. In fact, among those who have severe *Listeria* infection, the ratio of immunosuppressed to normal patients is probably greater than in any other bacterial infection with the possible exception of the *Nocardia* species.³

BACTERIOLOGY OF THE DISEASE

Listeria is a gram positive coccobacillus which is non-capsulated, a non-spore forming rod of 0.1 μ by 0.2 to 2.0 μ size with a curved body and rounded ends. They usually grow well on conventional media. Gray has recommended refrigeration at 4° C. to release the bacteria from their intracellular location. It has been recommended to use phenethyl alcohol which inhibits gram negative growth. The identification by proper biochemical and motility

studies is important and if all criteria are used the definitive identification is easy and virtually 100 percent. Some of the colonies produce B-hemolysis with a light green translucent appearance when viewed slightly tangentially.

The wet mounts show a tumbling motion of the bacteria which is characteristic. The biochemical tests employed are (1) catalase test with 3% hydrogen peroxide producing brisk evolution of oxygen, (2) a positive methyl red test, (3) highly reliable positive fermentation tests with glucose and salicin give the production of acid but no gas, and (4) inability to ferment Mannitol.

Due to multiplicity of cross reactions, no specific serological tests are helpful in diagnosis. By H and O antigen, 11 serotypes have been found and type 4B and 1 appear to be predominant in most of the cases reported in the United States. There seems to be no correlation between the antigenic type and geographic distribution or host specificity.

When stained in smears this organism will not grow on primary culture but does grow after 4 or 5 days or often after 30 to 50 days when held at 4° C. The ability to regain cultivation, a mechanism of rejuvenation, still remains a mystery.

The organism is a facultative intracellular parasite which has a high pathogenicity. The antibodies first to appear are IgM type which are later replaced by IgG.

In animals, this disease is manifested by mononucleocytosis and development of small necrotic foci in the internal organs. In man, the disease causes different systemic complications including a high incidence of abortions and stillbirths in women.¹⁶

TREATMENT

Different centers have reported varying experiences with the treatment with different antibiotics. Penicillin, Ampicillin, Tetracycline have been found to be effective against *Listeria*; however, except for Tetracycline, some reports of resistance have appeared. Due to its poor crossing of the blood brain barrier, cephalosporin is not a good drug of choice, in fact there have been case reports of the development of meningitis while the patients were being treated with the cephalosporin for systemic Listeriosis.⁸

The most important point is to start the therapy initially as soon as possible if Listeriosis is suspected and to switch promptly after positive identification is made and sensitivity testing has been completed to the appropriate antibiotic. The therapy must be continued at least one week after defervescence. Erythromycin also appears to be a good alternative. The dosages have been recommended as follows: Penicillin G, 20 million units per day either by continuous intravenous infusion or at 2 to 3 hour intervals; Tetracycline, 15 mg/kg body

weight per day; Erythromycin, about 75 mg/kg body weight per day. Ampicillin in a dosage of 12 to 18 gm/day also has been found useful.

PROGNOSIS¹³

Without prompt and adequate antibiotic therapy the *Listeria* meningitis is fatal in over 90% of the cases. Other forms of Listeriosis yield to the treatment very well. If acquired transplacentally, death of the fetus virtually always occurs. The development of a vaccine for use in domestic animals appears to be promising. Ultimately, the recognition and prompt treatment dictate the prognosis.

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Pulmonary Rehabilitation*

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The immense problem of advanced chronic bronchitis and emphysema (known collectively as chronic obstructive lung disease — COLD) is well known to pulmonary scientists, primary care physicians, and allied health workers alike.

By the time it is published, every measure of case rate, disability, and death is obsolete. But even though the true prevalence and economic impact may not be accurately known, it is patently obvious that the problem is massive.

Three separate studies from other institutions on the course and prognosis of COLD have indicated the following: the mean age of patients admitted to these studies ranged from 57 to 59; the FEV₁ (forced expired volume in one second) approximated 1.0 liter per second; and most patients were male.^{1,2,3} In each series, the course was progressive, with further deterioration of ventilatory function each year. Prognosis was roughly proportional to the degree of derangement of ventilatory function as judged by simple spirometry. Cor pulmonale carried a particularly adverse prognosis.

Simultaneous with the emergence of this dismal picture, a number of clinical investigators undertook new and innovative approaches to the care and rehabilitation of patients with advanced degrees of disease. The pioneering work of Barach (New York), Haas (New York), and Miller (Dallas) provided encouragement. At the University of Colorado Medical Center, as our program of pulmonary rehabilitation evolved and was formalized as an ongoing study in 1966, we enthusiastically added some of our own ideas.

This report briefly describes techniques useful in the broad context of pulmonary rehabilitation. It also offers a perspective on the effectiveness of a systematic approach to managing large numbers of patients with severe COLD. Experiences and results of our Colorado program are used liberally.

DEFINITION OF PULMONARY REHABILITATION

The following definition — workable and useful — was adopted by the committee on pulmonary

rehabilitation of the American College of Chest Physicians at its annual meeting in 1974:

"Pulmonary rehabilitation may be defined as an art of medical practice wherein an individually tailored, multi-disciplinary program is formulated which through accurate diagnosis, therapy, emotional support, and education, stabilizes or reverses both the physio- and psychopathology of pulmonary diseases and attempts to return the patient to the highest possible functional capacity allowed by his pulmonary handicap and overall life situation."

USEFUL MODALITIES OF CARE

Patient Education

Fundamental to the successful management of patients with *any* form of disease is careful and comprehensive patient indoctrination.

Patients must understand the disease process, its pathogenesis, symptoms of exacerbation, and the goals and details of therapy. The enlightened patient must become involved in his own care, with family members also a fundamental part of the health care team. Personalized and detailed instructions should be provided by a physician or, even better, a nurse or therapist who may have more time and patience in presenting the complex and difficult material. Often these individuals have the necessary time to answer the many questions that inevitably arise in the minds of the motivated patient or family. Booklets and patient care manuals⁴ supplement the initial personalized instruction, and audio-visual aids are useful. Repeat visits for reinstruction also are frequently necessary.

Pharmacological Agents

The following three groups of pharmacologic agents play an important, and at times fundamental, role in the management of patients with severe obstructive lung disease.

1. Antibiotics

Although the initial insult to the tracheobronchial tree may be a viral invasion, secondary bacterial involvement is common. The expected organisms are *H. influenza* and *S. pneumonia*. This is the reason that tetracycline, for more than 20 years, has been so useful in the management of patients with severe chronic obstructive lung disease. Today there are *S. pneumonia* strains resistant to tetracycline, but these drugs remain clinically useful. Ampicillin is probably the first choice today for patients who are not sensitive to penicillin derivatives. Unfortunately a number of *H. influenza* strains resistant to ampicillin are also emerging. Alternative treatment includes the use of trimethoprim with sulfamethoxazole or

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even chloramphenicol, which is highly effective against *H. influenza*. These latter two drugs should be chosen under strict physician supervision. By contrast, it has been commonplace to offer patients a home supply of either tetracycline or ampicillin to take at the first sign of a "deep chest infection," characterized by increased cough, fever, and purulent (yellow or green) sputum. The routine culturing of sputum is unnecessary and, in fact, inaccurate in patients with chronic bronchitis, and the empiric use of ampicillin or tetracycline is now established therapy.

2. *Bronchodilator Drugs*

Patients fulfilling the American Thoracic Society definition of emphysema and chronic bronchitis⁵ may have a bronchospastic component. Thus, the systematic use of both inhaled and oral bronchodilating drugs may be useful. At the University of Colorado Medical Center, it has been our general practice to use oral methylxanthines (oxtriphylline [Choleryl[®]] or aminophylline if tolerated) to tolerance in patients with no gastrointestinal upset and/or oral ephedrine when patients gain symptomatic benefits. (Use of inhaled bronchodilators as part of a bronchial hygiene program is described later.)

3. *Corticosteroids*

Surprisingly, patients who appear to have emphysema and chronic bronchitis may have a significant reversible component during comprehensive therapy that includes corticosteroid drugs. Approximately 10 percent of the patients within our rehabilitation series had such a significant reversible component, and in most cases, it occurred coincident with the use of corticosteroid drugs.⁶ It is our feeling that corticosteroids should be tried for approximately two weeks. Response to them is suggested by improvement in ventilatory function tests, blood gases, and the patient's symptoms. Steroids should not be continued without good reason.

Preventive Therapy Against Influenza

Almost every fall in recent years, "A" strains of influenza have caused epidemics or pandemics. Thus, the regular use of polyvalent vaccine each fall should be routine. We have also found that in patients at high risk or highly exposed, the use of the oral preventive drug amantadine has been safe and useful.

Bronchial Hygiene

Impaired clearance of retained mucus is an underlying problem common to most patients with severe obstructive lung disease. Thus, measures to dilate bronchi, promote mucociliary clearance, and remove secretions should be valuable on theoretic grounds. We regularly used a technique called

"bronchial hygiene." Briefly, this is the inhalation of a sympathomimetic amine (usually Bronkosol[®], containing isoetharine and phenylephrine), followed by moisture inhalation, followed by expulsive coughing and/or postural drainage. The technique of delivering these agents and the devices used in the home are beyond the scope of this discussion. We most commonly use simple devices, however, such as hand bulb or pump-driven nebulizers, and occasionally metered-dose devices for morning and evening bronchial hygiene sessions. Occasionally, in the most obstructed individuals, IPPB appears to be more effective. Thus far, however, no controlled study has shown that IPPB therapy, with or without bronchodilators, is in any way more effective than systematic therapy without these more expensive devices.^{7,8,9} We remain enthusiastic about simple methods of bronchial clearance, as do our patients.

Breathing Training and Physical Reconditioning

Studies in our laboratory indicate that the technique of slow abdominal diaphragmatic breathing with exhalation against pursed lips improves ventilatory efficiency and CO₂ elimination in patients with severe disease more commonly than other methods of augmented breathing.¹⁰ Elaborate controlled studies of pursed-lip breathing have also revealed that this technique not only helps relieve dyspnea but, in addition, consistently and significantly decreases respiratory rate and minute ventilation, increases tidal volume, and reduces the oxygen ventilation equivalent (O₂V).¹¹ Also, arterial oxygen tension and CO₂ tension are improved at rest. This technique, frequently learned spontaneously by patients, has been widely used and claimed by pioneers of rehabilitative care for many years (Barach),¹² and almost any patient will affirm that it relieves dyspnea. From all this, we have concluded that pursed-lip breathing is an effective pattern of respiration.

Physical exercise almost always improves exercise tolerance in patients with marked dyspnea on exertion. This improvement can be sustained by brief periods of walking each day, and at times a marked improvement in exercise tolerance with greatly reduced dyspnea are the rewards. For example, *Figure 1* shows what happened to a 61-year-old man after two weeks of training: There was marked improvement in rate and grade walked, as well as stairs climbed to the point of intolerable dyspnea or a pulse rate greater than 120. Although his pulmonary function remained unchanged, there was considerable increase in work capacity as the result of such training.

Oxygen

The role of home oxygen in the management of patients with advanced obstructive lung disease has received considerable attention lately, not only in this country, but also in the United Kingdom.^{13,14} There has been remarkable agreement, both at

WALK TOLERANCE DURING GRADED EXERCISE

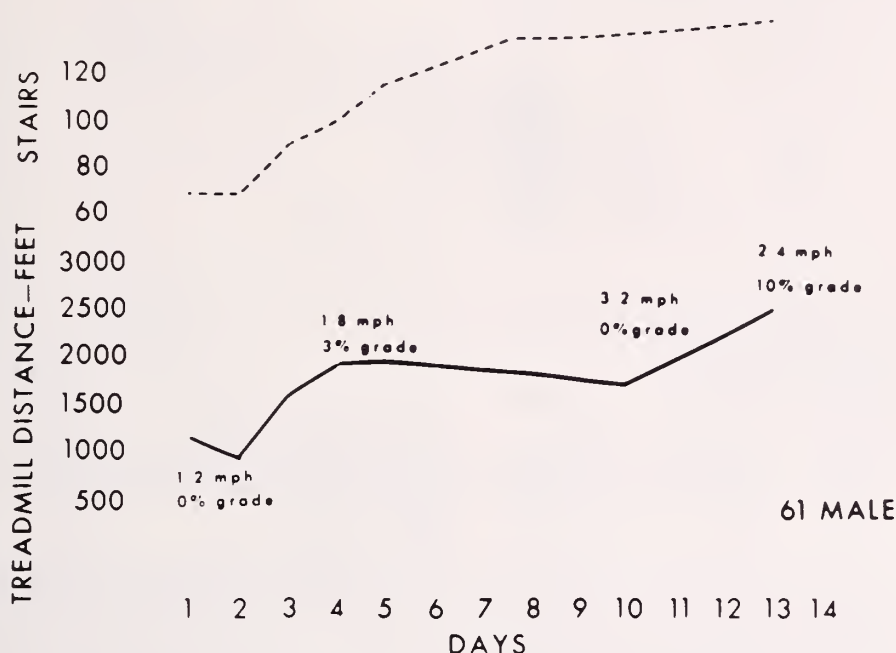


FIG. 1 Walk tolerance to dyspnea or pulse rate of 120 for a 61-year-old male with FEV₁ of 0.9 L. A marked increase in walk tolerance occurred following 30-minute training periods over a two-week time span.

Denver's altitude and at sea level, that reactive pulmonary hypertension can be relieved in *some but not all* individuals,^{13,14} and that polycythemia can be controlled.¹⁵ Careful, controlled double-blind studies have further shown that cognitive function is markedly improved with oxygen as compared to air.¹⁶ Recent studies by Lilker in Toronto¹⁷ have established that, in selected patients, exercise tolerance and the feeling of well-being during exercise are considerably better with an ambulatory oxygen system (the Linde Liquid Oxygen Walker).

THE COLORADO REHABILITATION PROGRAM

Following original pilot studies, our group embarked upon a systemized outpatient and home care rehabilitation program in 1966. The description of our methodology and preliminary results has been reported elsewhere.¹⁸ Briefly, we selected 182 patients with severe COLD who were *clinically* ill and who either were referred to us or came after receiving word-of-mouth information about our newly announced rehabilitation program for *severe* respiratory cripples. All patients fulfilled the diagnostic criteria of the American Thoracic Society,⁵ and every effort was made to exclude patients with reversible airways obstruction. Patients were also excluded if they had other significant disease such as malignancy or a profound metabolic disorder that would interfere with prognosis or participation in the program. Patients had to have a clear claim of

disability (always subjective) and a measured FEV₁ or MVV of less than 50 percent of predicted for their age and sex. Patients were accepted into the program *consecutively with no restrictions* as to severity of disease, age, sex, ethnic origin, previous failure to comply with therapy, or recent hospitalization. Some patients were already receiving oxygen when they entered the program. Eleven patients came in wheelchairs.

All patients received a formalized program of indoctrination and followed physician-ordered, tailor-made programs which always included bronchial hygiene (usually with simple techniques), breathing training, efforts at exercise conditioning, and appropriate pharmacologic agents (usually antibiotics). In selected cases, home oxygen was given. A total of 53 of the 182 patients received oxygen, and 33 of the 53 received continuous oxygen.

Patients were seen at regular intervals by the author or other members of the team. Thus, we have had the opportunity to follow this original group of patients continuously and to observe them for more than eight years. During this period, the approach to therapy has been relatively unchanged.

In *Table 1* are listed the background factors of those entering the rehabilitation program. (Note that the average age was 61, and the FEV₁ was 0.94 L.)

As a further refinement in determining the results of our Colorado rehabilitation program, we used

TABLE 1

CHARACTERISTICS OF 182 PATIENTS AT ENTRY TO REHABILITATION PROGRAM			
	Average	SD*	Range
Age (Yrs.)	61	9	33-81
Sex	87.3% Male		
Wt. (Lbs.)	142	29	88-265
Ht. (In.)	67.9	3.0	58.4-75
VC (Liters)	2.58	0.79	1.22-5.17
FEV ₁ (L)	0.94	0.38	0.26-2.21
MMEF (L/sec.)	0.41	0.22	0.11-1.77
MVV (L/min.)	35.5	15.1	6.4-80.9

*Standard deviation.

TABLE 2

PATIENTS IN REHABILITATION STUDY VS. PATIENTS ON EMPHYSEMA REGISTRY (Mean Values in Matching)			
	Patients in Rehabilitation Study	Patients on Emphysema Registry*	2 Tailed T-Test
Age	58.5	57.9	NS
Height	175	175	NS
FEV ₁	1.08	1.15	NS
SAO ₂	89	88	NS

*Courtesy of Roger S. Mitchell, M.D.

computer techniques to match 72 male patients from our study with male patients on an emphysema registry (organized and supervised by Roger S. Mitchell, M.D.) where the outcome was known. The patients were also matched by age, height, FEV₁, and oxygen saturation breathing room air (Table 2). Although there was no proof, there was the strong suggestion that survival was improved in patients in our Colorado rehabilitation program. See Table 3.

IMPACT OF A PULMONARY REHABILITATION PROGRAM

It is extremely important to be realistic and forthright about the results of a program of pulmonary rehabilitation. With this in mind, I would like to describe here what I believe we have accomplished in the Colorado program.

Improved Symptom Complex

We secured the services of a disinterested psychologist who studied a subseries of the patients. Thirty patients were evaluated upon entry into the program and again after one year. Significant improvement was found in objective signs of affective distress, i.e., a significantly reduced score for anxiety, depression, and somatic concern (Table 4). Relative improvement in other symptoms and no change in dependency behavior or psychopathology were also found. In short, the patients felt better and performed better in the testing situation.¹⁹ See Table 4 again.

Improved Exercise Tolerance

There was an impressive and highly significant

TABLE 3

CUMULATIVE SURVIVAL (N = 72)		
Year	Patients in Rehabilitation Study %	Patients on Emphysema Registry %
1	97	90
2	90	83
3	78	76
4	68	63
5	56	47
6	49	36
7	46	33
8	44	29

TABLE 4

MEASURED IMPROVEMENT			
	1969	1970	P*
Patient Symptom Trend**	22.7	14.9	<.01
MD Evaluation of Symptom Trend**	20.2	15.6	<.01
Patient Affective Distress**	50.6	42.7	<.01
Walk Tolerance (Ft.) at Increasing Rates and Grades	400	1094	<.001
MVV (L/min.)	33.4	38.6	<.01

*P = Significance as measured by single-tailed T-test.

**Low scores indicate a lower symptom trend.

TABLE 5

REDUCTION IN HOSPITAL DAYS* (All Patients)	
Year	Total Hospital Days (Days/Patient/Year)
0	13.6
1	9.3
2	8.1
3	6.0
4	7.5
5	5.9
6	6.0
7	2.2

*Data analysis courtesy of Steven A. Sahn, M.D.

TABLE 6

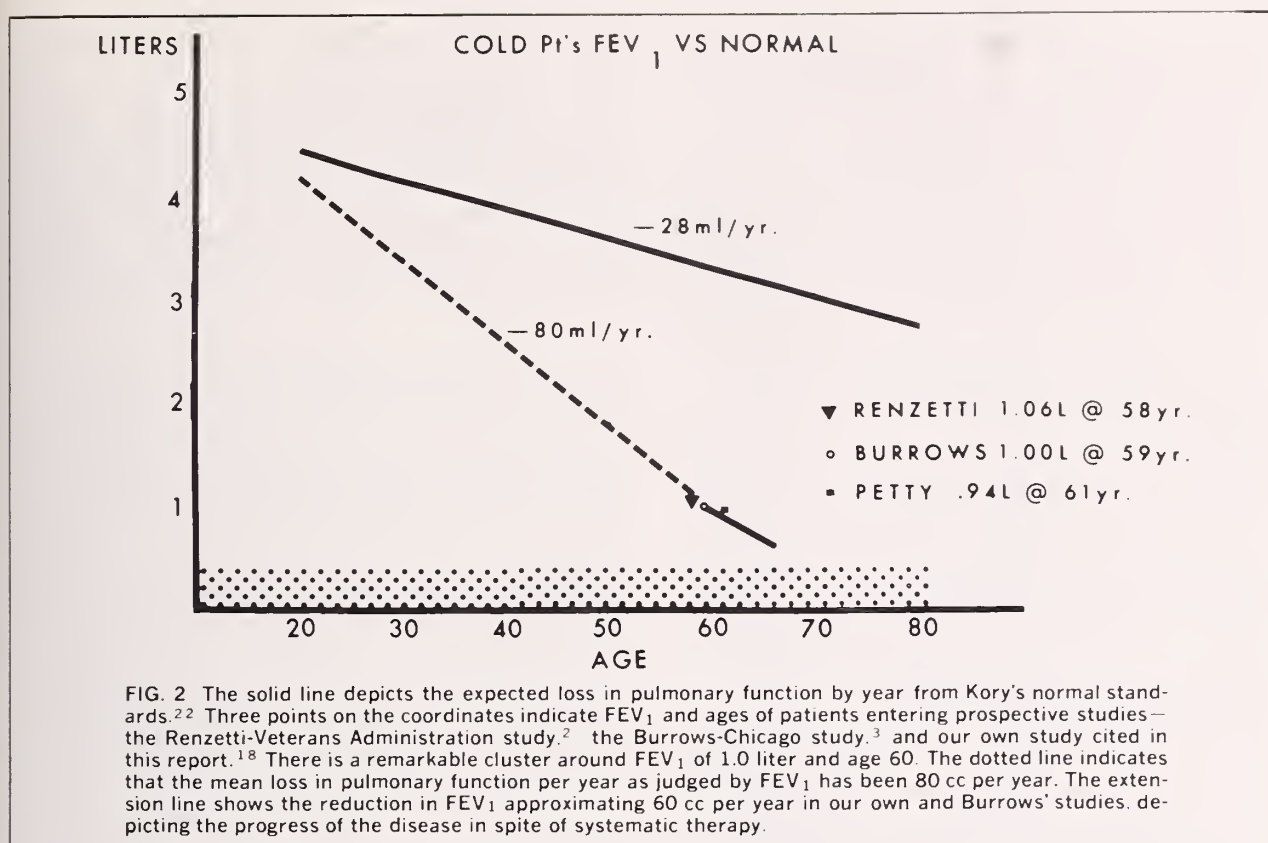
HOSPITAL DAYS*					
Number	Year Before Program	1st Year	2nd Year	3rd Year	4th Year
64	631	309	350	—	—
61	563	247	343	428	—
44	529	145	270	278	207

*Data analysis courtesy of Leonard D. Hudson, M.D.

improvement in exercise tolerance in another representative series of 129 patients. The improvement was sustained for up to two years.^{19,20} This improved exercise tolerance could almost always be translated into improved activities of daily living.

Reduction in Hospital Days

In Tables 5 and 6 is shown the reduction in hospital days of a subgroup of patients who had carefully kept hospital records prior to program entry. For each group of patients, a reduction in hospital days



compared to the prior year's days could be found. The number in each group decreased due to deaths in the third and fourth years of followup. Looking at the group as a whole, the *total hospital days* decreased from 13.6 per patient per year before program entry down to 2.2 per patient per year in the seventh year. This is due, in part, of course, to the fact that the sickest patients died during the course of the study, thus leaving a residual population requiring less hospitalization.

Gainful Employment

Although we made every effort to assist patients either in maintaining or regaining employment, the effort was only moderately successful.²¹ We were more successful in helping patients retain employment than in vocational rehabilitation. Vocational success was related to the energy requirements of the job, job adjustment, and exercise tolerance. Those who were able to maintain or regain employment had the same degree of physiologic impairment as those who did not work.²¹ Oxygen assisted in vocational adjustment in selected cases.

Progress of Disease

We are not at all sure that we have altered the natural history of the disease, including the rate of pulmonary function deterioration. *Figure 2* shows that data points (from the Burrows-Chicago study, the Renzetti-Veterans Administration study, and our own data from the series reported in this article) cluster around age 60 and FEV₁ of 1 L. The dotted

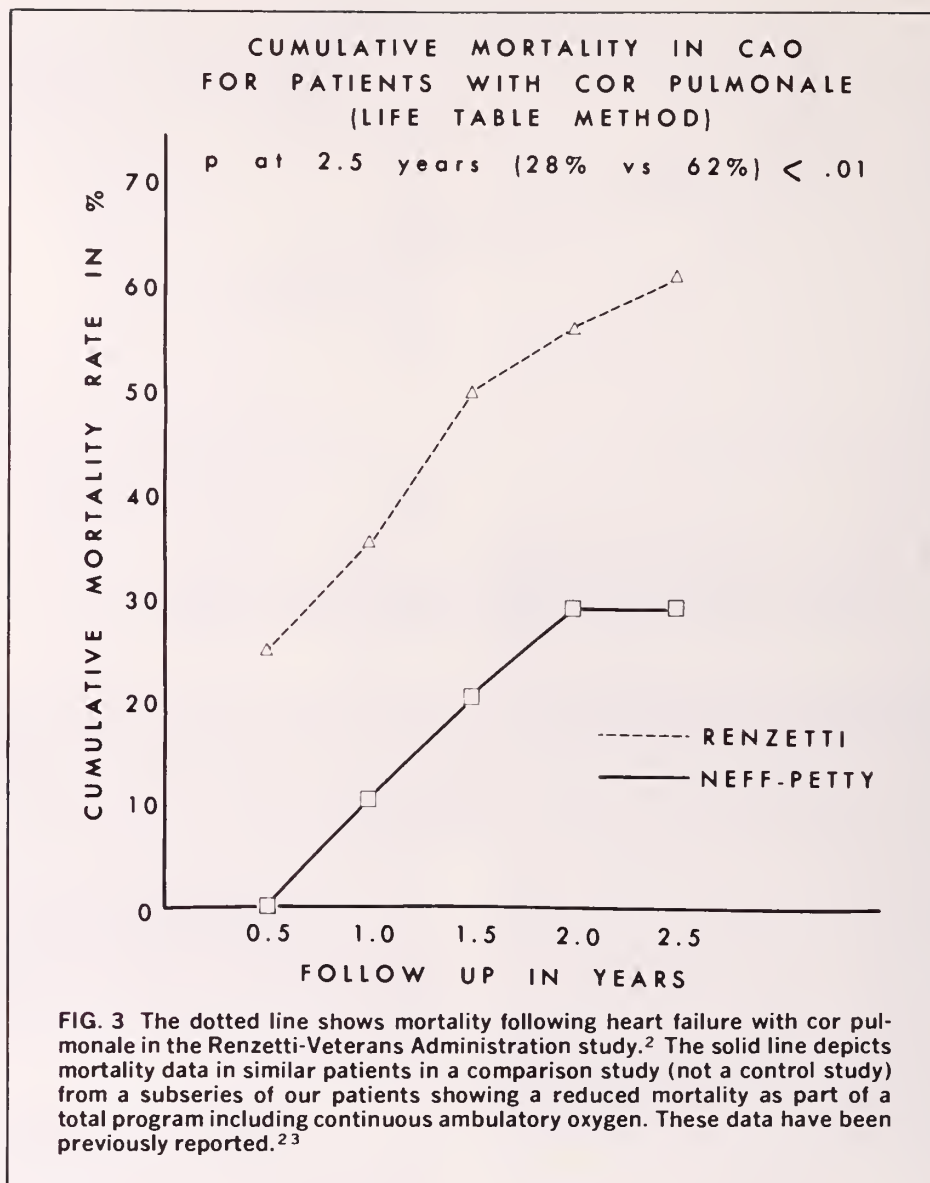
TABLE 7

FEV ₁ CHANGE PER YEAR* (All Surviving Patients)	
Year	Δ FEV ₁ (cc)
1	— 42
2	— 44
3	— 104
4	— 61
5	— 35
6	— 17
7	— 69
8	— 9
GRAND MEAN	— 52

*Data courtesy of Steven A. Sahn, M.D.

line suggests that if these patients (of average height) were normal at age 20, their loss of pulmonary function averaged 80 cc per year. We do not contend, however, that the loss is pulmonary function is linear. The extension of this solid line is from the Burrows-Chicago study that shows the progress of disease approximating 60 cc per year in spite of care at the University of Chicago clinics. The normal reduction in FEV₁ as a consequence of age (from Kory's data)²² is shown by the solid line; these data are presented for perspective.

In our own group of surviving patients, the loss in pulmonary function per year over eight years is presented in *Table 7*. Thus, the loss in pulmonary function as judged by FEV₁ is obvious and averaged 52 cc per year. There is no suggestion, therefore,



that we have slowed the deterioration in ventilatory function in the entire series compared to data from other studies. Similar progress of disease — 59 cc per year — has been reported from the Nebraska program (Irving Kass, University of Nebraska, personal communication).

Survival

The value of medical care cannot be measured solely by survival. However, in individual cases, survival may be improved by aggressive management of acute respiratory failure. Additionally, in a subseries of patients with cor pulmonale managed with continuous oxygen as part of a total rehabilitation program, there was a suggestion of improved survival when compared to the survival rate in similar patients not receiving oxygen or a similar type of rehabilitation program. This has been described in a report published earlier.²³ See Figure 3.

SUMMARY

The value of systematic care programs is today generally recognized. The Inter-society Commission on Heart Disease Resources has recently described programs for the smaller community hospital, the large multispecialty clinic, and the university referral center.²⁴ The approach to care and the details of each program at the three different levels are well delineated in the report.

I must conclude this review with the clear expression of enthusiasm concerning the benefits of systematic care for patients with advanced obstructive lung disease. Certainly we must turn our attention to earlier diagnosis and to studies of the effectiveness of care in less severely affected individuals. It seems clear at this time, however, that the type of approach described herein is effective from the standpoint of reducing the symptom complex and improving the life style of patients, including their

ability to exercise and maintain a more satisfying life.

There has been no attempt in this review to summarize costs, which are not high except for the need for continuous oxygen. Since most of the care can be provided by the non-physician, the type of program described herein seems appropriate for those interested in serving the sick, in this case individuals suffering from advanced chronic bronchitis and advanced emphysema.

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Pharmacotherapy of Inflammatory Bowel Disease

RICHARD C. GARDNER, M.D.

ABSTRACT

Inflammatory bowel disease is a poorly understood, nonspecific inflammatory process of the gastrointestinal tract that includes two well-described clinical entities — ulcerative colitis and Crohn's disease. The mortality and morbidity associated with this condition have been drastically reduced in the past several decades by the vast improvement in general medical and surgical management and by the introduction of specific drugs that empirically have been found to be of therapeutic benefit. Sulfasalazine and topical (rectal) corticosteroids are effective in many patients with mild distal ulcerative colitis. Maintenance sulfasalazine therapy significantly reduces the relapse rate in ulcerative colitis. Systemic corticosteroids have improved the survival rate of patients with moderate and severe ulcerative colitis. Both sulfasalazine and corticosteroids appear to be effective in Crohn's disease but require further investigation. Azathioprine is currently under evaluation and may be effective in selected patients with Crohn's disease.

Inflammatory bowel disease has become a major diagnostic and therapeutic challenge for the physician in the past two decades. Although significant strides have been made during this period in advancing our descriptive knowledge and classification of inflammatory bowel disease, our understanding of its etiology has not progressed beyond the speculative stage. Furthermore, it is far from clear whether the two major types of inflammatory bowel disease — namely, ulcerative colitis and Crohn's disease — represent distinct and separate entities or are variants of a spectrum of the same basic disease process.

Notwithstanding the many unanswered questions concerning the basic pathophysiological mechanisms involved in this disease, a sound system of therapeutics has evolved over the past several decades. These advances were based primarily upon the empirical trial and error method of assessing the effectiveness of pharmacological agents as well as upon improved general medical care and better rec-

ognition of the indications for appropriate surgical intervention.

The guidelines of the therapeutic approach to inflammatory bowel disease rests upon five important considerations: (1) exclusion of the various treatable infectious and iatrogenic causes of colitis and ileitis, (2) differentiation, where possible, between ulcerative colitis and Crohn's disease according to accepted diagnostic criteria, (3) assessment of the severity of the disease in each individual, (4) the recognition of the local and systemic complications, and (5) adequate assessment of the possible emotional stresses and psychiatric abnormalities unique to each patient.

This review will examine the historical background upon which our current approach to inflammatory bowel disease is based, and, after a brief description of the characteristics that distinguish ulcerative colitis and Crohn's disease, will consider the rationale for the pharmacotherapy and management of each of these disease entities.

HISTORICAL PERSPECTIVE

Just over 100 years ago, the first description of ulcerative colitis appeared in the literature, distinguishing it from the known infectious causes of colitis.¹ It was not until 57 years later, in 1932, that an inflammatory disease of the distal small intestine was first recognized as distinct from tuberculous enteritis, and this was subsequently referred to as regional enteritis or Crohn's disease.² Nearly three decades later, in 1960, it became appreciated that Crohn's disease also could involve the colon and that it was important to distinguish this form of colitis from ulcerative colitis.^{3,4}

Pharmacotherapy was first introduced in the 1940's, when it was fortuitously discovered that sulfasalazine had a beneficial effect on the symptoms of colitis while it was being evaluated in patients with rheumatoid arthritis, some of whom had coexisting ulcerative colitis. Since then, several prospective controlled studies have confirmed this effect and, in addition, have demonstrated a marked reduction in the relapse rate of ulcerative colitis in those patients maintained on sulfasalazine for long periods of time.^{5,6}

The second major breakthrough in the treatment of inflammatory bowel disease occurred in the 1950's when it was reported that corticosteroids and

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TABLE 1

SEVERITY OF ULCERATIVE COLITIS

	Mild	Moderate	Severe
Percentage of Patients	60%	25%	15%
Extent of Disease	Often Rectosigmoid	Often Universal	Often Universal
Fever	Absent	99°-101°F	101°-104°F
Tachycardia	Absent	80-100/min	100-140/min
Bowel Movements (no./day)	Less than 4	4-6	More than 6
Amount of Blood in Stool	Scant	Moderate	Profuse
Weakness and Fatigue	Absent	Slight	Profound
Abdominal Tenderness	Absent	Slight	Often Severe
Anorexia and Weight Loss	Absent	Slight	Severe
Anemia and Hypoalbuminemia	Absent	Slight	Profound
Toxic Megacolon	Nil	At Risk	At Risk

ACTH (corticotropin) were beneficial in acute attacks of ulcerative colitis.^{7,8} However, maintenance steroids were subsequently found not to be effective in prolonging remissions and preventing serious relapses.⁹ Favorable results with steroids and ACTH were also reported in the treatment of Crohn's disease in the 1960's.^{10,11}

Since the introduction of steroids in the 1950's the overall mortality in ulcerative colitis appears to have been reduced by approximately 50%. Although this significant drop in mortality has been in part due to the use of steroids in reducing the immediate mortality of the acute attack of ulcerative colitis, vastly improved general medical management and the use of early elective colectomy in refractory cases may have contributed in an even greater way. The mortality and morbidity of Crohn's disease have been less favorably affected in the past two decades due in part to the chronicity and debilitating complications of the disease and its high recurrence rate following surgery.

DIAGNOSIS AND DESCRIPTION OF EACH DISEASE

Ulcerative Colitis

Ulcerative colitis is a chronic disease characterized by acute attacks of rectal urgency, tenesmus, diarrhea, and rectal bleeding of varying severity. Although the majority of patients (60-75%) experience multiple acute symptomatic relapses and remissions, there are some patients (10-15%) who have continuous symptoms over extended periods of time. Only a few patients (5-10%) have an initial attack without subsequent relapses.¹²

Pathologically, the inflammatory process is usually limited to the colonic mucosa but may extend into the adjacent submucosa. Anatomically, the rectum and left colon are most often involved, but inflammation of the entire colon is not uncommon. Significant small bowel disease does not exist, but mild, superficial inflammation of the distal portion of the ileum may exist ("backwash ileitis").

The diagnosis is based primarily upon the clinical history of tenesmus and bloody diarrhea, the demonstration of diffuse proctitis by proctosigmoidoscopy, and the exclusion of infectious colitis by stool bacterial cultures and by appropriate examinations for ova and parasites. A rectal biopsy is

helpful in confirming mucosal inflammation and ruling out amebic colitis. The finding of ulcerations on barium enema examination supports the diagnosis and defines the extent of the disease.

As we will see later, the treatment of ulcerative colitis is dependent upon the severity of disease in each individual. The majority of patients (60%) present with mild disease with only two to four bowel movements per day, minimal rectal bleeding, and no constitutional symptoms.¹² Most of these patients have disease limited to the rectosigmoid, but about 15% will eventually extend their disease and experience more severe symptoms.¹³ Approximately 25% of patients with ulcerative colitis will present with moderate disease, the symptoms of which include four to six watery bowel movements per day, considerable blood in the stool, low-grade fever (99°-101°F), some weakness and fatigue, intermittent anorexia, abdominal cramps, and mild anemia, leukocytosis and low serum albumin. Many of these patients later develop a more severe form of colitis. Finally, about 15% of patients present with severe colitis, characterized by greater than six watery, bloody bowel movements per day, high fever (101°-104°F), tachycardia and profound weakness, fatigue, anorexia, and weight loss. Examination reveals marked pallor and abdominal tenderness. Marked leukocytosis, anemia and hypoalbuminemia are usually present (see Table 1).

The three most serious complications of ulcerative colitis are toxic megacolon, colonic perforation, and cancer of the colon, each of which is associated with a high mortality. Toxic megacolon is defined as an acute, massive dilatation of the colon accompanied by high fever (103°-106°F), tachycardia, prostration, abdominal distention and tenderness. A plain supine X-ray film of the abdomen is diagnostic, revealing a massively dilated air-filled colon. If left untreated, toxic megacolon will eventually lead to colonic perforation. Perforation of the colon is a complication of moderate or severe colitis and may occur in the absence of toxic megacolon, especially in the elderly.

The risk of cancer of the colon in patients with ulcerative colitis is related to three variables: age of onset, extent of disease, and duration of illness. Only patients with total colonic involvement appear

TABLE 2

DISTINGUISHING FEATURES OF ULCERATIVE COLITIS AND CROHN'S DISEASE		
	<i>Ulcerative Colitis</i>	<i>Crohn's Colitis</i>
<i>Symptoms</i>		
Diarrhea	Severe	Moderate
Blood in Stool	Common	Unusual
Abdominal Pain	Unusual	Common
Rectal Urgency and Tenesmus	Common	Unusual
<i>Site of Involvement</i>		
Rectum	95%	50%
Ileum	—	Common
Segmental Distribution	Rare	Common
<i>Complications</i>		
Toxic Megacolon	5-20%	Less than 5%
Fistulae	Rare	Common
Cancer	Increased Risk (>10 years of disease)	?
Strictures (benign)	Rare	Common
<i>Histological Features</i>		
Inflammation	Mucosal	Transmural
Granulomas	Absent	Present (50-60%)
Sinus Tracts	Absent	Common

to be at increased risk, and the incidence of cancer rises sharply after ten years of disease, especially with onset of disease in childhood. For example, ulcerative colitis that begins in the second decade of life carries about a 3% risk of cancer at ten years' duration of illness, and the cumulative risk increases by 2% every year thereafter.¹⁴ Disease acquired in adulthood also confers a high cancer risk with an estimated cumulative risk of as high as 40% at 25 years of disease.¹⁵ Frequent examination of the stool for occult blood and periodic barium enema examination are mandatory for the early detection of cancer in longstanding ulcerative colitis. The use of plasma assays for carcinoembryonic antigen,¹⁶ the examination of rectal biopsies for premalignant mucosal changes,¹⁷ and the use of fiberoptic colonoscopy are currently under study as additional diagnostic aids in the early detection of cancer.

Various systemic complications are common in ulcerative colitis and include arthritis, sacroileitis, uveitis, chronic liver disease, erythema nodosum, pyoderma gangrenosum, thrombophlebitis, and aphthous stomatitis.

Crohn's Disease (Regional Enteritis, Granulomatous (Ileo-) Colitis)

Crohn's disease is also a chronic disease but differs from ulcerative colitis in several important respects (see Table 2). Clinically, the onset of symptoms is usually insidious and is characterized by watery, non-bloody diarrhea, abdominal pain and low-grade fever (99°-101°F). The symptoms are slowly progressive, often over many months and are accompanied by gradual weight loss, anemia and debility. Acute attacks are unusual but can occur

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Before prescribing, please consult complete product information, a summary of which follows:

Indications: In adults, urinary tract infections complicated by pain (primarily pyelonephritis, pyelitis and cystitis) due to susceptible organisms (usually *E. coli*, *Klebsiella-Aerobacter*, *Staphylococcus aureus*, *Proteus mirabilis*, and, less frequently, *Proteus vulgaris*) in the absence of obstructive uropathy or foreign bodies. **Note:** Carefully coordinate *in vitro* sulfonamide sensitivity tests with bacteriologic and clinical response; add aminobenzoic acid to follow-up culture media. The increasing frequency of resistant organisms limits the usefulness of antibacterials including sulfonamides. Measure sulfonamide blood levels as variations may occur; 20 mg/100 ml should be maximum total level.

Contraindications: Children below age 12; sulfonamide hypersensitivity; pregnancy at term and during nursing period; because Azo Gantanol contains phenazopyridine hydrochloride it is contraindicated in glomerulonephritis, severe hepatitis, uremia, and pyelonephritis of pregnancy with G.I. disturbances.

Warnings: Safety during pregnancy not established. Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been reported and early clinical signs (sore throat, fever, pallor, purpura or jaundice) may indicate serious blood disorders. Frequent CBC and urinalysis with microscopic examination are recommended during sulfonamide therapy.

Precautions: Use cautiously in patients with impaired renal or hepatic function, severe allergy, bronchial asthma; in glucose-6-phosphate dehydrogenase-deficient individuals in whom dose-related hemolysis may occur. Maintain adequate fluid intake to prevent crystalluria and stone formation.

Adverse Reactions: *Blood dyscrasias* (agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia); *allergic reactions* (erythema multiforme, skin eruptions, Stevens-Johnson syndrome, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis); *G.I. reactions* (nausea, emesis, abdominal pains, hepatitis, diarrhea, anorexia, pancreatitis and stomatitis); *CNS reactions* (headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo and insomnia); *miscellaneous reactions* (drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L.E. phenomenon). Due to certain chemical similarities with some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia. Cross-sensitivity with these agents may exist.

Dosage: Azo Gantanol is intended for the acute, painful phase of urinary tract infections. *Usual adult dosage:* 2 Gm (4 tabs) initially, then 1 Gm (2 tabs) B.I.D. for up to 3 days. If pain persists, causes other than infection should be sought. After relief of pain has been obtained, continued treatment with Gantanol (sulfamethoxazole) may be considered.

NOTE: Patients should be told that the orange-red dye (phenazopyridine HCl) will color the urine.

Supplied: Tablets, red, film-coated, each containing 0.5 Gm sulfamethoxazole and 100 mg phenazopyridine HCl—bottles of 100 and 500.



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BRIEF SUMMARY OF PRESCRIBING INFORMATION

***INDICATIONS.** Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

Effective: Management of nausea and vomiting and dizziness associated with motion sickness.

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Final classification of the less than effective indications requires further investigation.

CONTRAINDICATIONS. Administration of Antivert (meclizine HCl) during pregnancy or to women who may become pregnant is contraindicated in view of the teratogenic effect of the drug in rats.

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Meclizine HCl is contraindicated in individuals who have shown a previous hypersensitivity to it.

WARNINGS. Since drowsiness may, on occasion, occur with use of this drug, patients should be warned of this possibility and cautioned against driving a car or operating dangerous machinery.

Usage in Children: Clinical studies establishing safety and effectiveness in children have not been done; therefore, usage is not recommended in the pediatric age group.

Usage in Pregnancy: See "Contraindications."

ADVERSE REACTIONS. Drowsiness, dry mouth and, on rare occasions, blurred vision have been reported.

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and may be confused with acute appendicitis.

Pathologically, the inflammatory process is *transmural*, frequently with sinus tracts and fistulae extending beyond the intestine into adjacent structures. Noncaseating granulomas are found on histologic examination in about 60% of cases in the intestine as well as in mesenteric lymph nodes. Anatomically, the distal ileum and right colon are most often involved, but the disease frequently may extend proximally in the small intestine and distally in the colon, often in segmental distribution with normal bowel separating diseased segments ("skip areas"). The rectum is often spared, with little or no proctitis in over 50% of cases of granulomatous colitis. Perianal sepsis, however, is common, and patients may present with a perirectal abscess or a draining fistula.

The diagnosis is based upon the characteristic history, physical examination, proctosigmoidoscopy, rectal biopsy, and barium X-ray studies of the entire gastrointestinal tract. Physical examination may reveal a tender, abdominal mass and a perianal fistula or abscess. Proctosigmoidoscopy may be normal or show a patchy proctitis, often with discrete ulcerations scattered throughout the rectum. Rectal biopsy is helpful in documenting the presence of submucosal inflammation and granulomas. Barium enema is valuable in demonstrating fistulae, segmental involvement, and ileal disease, and in distinguishing Crohn's disease from diverticulitis. Upper gastrointestinal series and small bowel X-rays may reveal involvement of the esophagus and stomach (rare) or segmental disease in the proximal small intestine.

Assessment of severity of disease in Crohn's disease is based primarily upon the extent of disease, the number and type of complications, and the degree of chronic inanition and debility, rather than severity of onset as in ulcerative colitis. Local complications include enteric and perirectal fistulae, intra-abdominal sepsis, and intestinal obstruction, all of which may require surgical intervention. Malabsorption of vitamin B₁₂ and bile salts may result from severe ileal disease, and more marked steatorrhea may occur when proximal small bowel disease is present in addition to bile salt deficiency. Toxic megacolon, intestinal perforation, and cancer of the colon may occur in Crohn's disease but are much less common than in ulcerative colitis. The systemic complications listed under ulcerative colitis are also common in Crohn's disease, and in addition, renal and gallbladder calculi are frequent, especially in patients with ileal disease. Longstanding disease may be associated with amyloidosis.

Indeterminate Group

Approximately 20-25% of patients with inflammatory bowel disease of the colon are difficult to classify as either ulcerative colitis or Crohn's disease.^{18,19} Clinically and radiologically, these patients present with a significant overlap of features

that are typical of both ulcerative colitis and Crohn's disease. Pathologically, the inflammatory process extends deeper into the colonic wall (e.g., into the muscularis propria and serosa) than is usually seen in ulcerative colitis, yet lacks the marked transmural thickening, sinus tracts and granuloma which are characteristic of Crohn's disease. The presence of this group of patients supports the widely held view that classical ulcerative colitis and Crohn's disease are at ends of a spectrum of the same basic disease process.

PHARMACOTHERAPY AND MANAGEMENT

Ulcerative Colitis

Mild Disease. Sulfasalazine* (Azulfidine,[®] Salazoprin,[®] SAS 500[®]) should probably be the first drug of choice in all patients with mild disease limited to the rectosigmoid, since it has been shown to be effective in the majority of these patients, obviating the need for other medication.^{5,6}

The usual recommended daily dose of sulfasalazine is 2-8 gms in four divided doses. It is important to initiate treatment with a low dose, usually 0.5 gm two to four times a day given with antacids or meals, and gradually increase the medication by 0.5 gm - 1.0 gm every one to two days until a total of 4-8 gms per day is reached. This approach will greatly minimize the frequency of headache, nausea and vomiting, which are common side effects of the drug and appear to be dose related.^{6,20} Other side effects, such as skin rash, hemolytic anemia (secondary to partial G6PD deficiency in red blood cells) and bone marrow suppression are manifestations of non-dose related idiosyncratic reactions and may necessitate withdrawal of the drug.

Once remission has occurred, as judged by improvement both in symptoms and proctosigmoidoscopic appearance, the dosage of sulfasalazine may be reduced gradually over several weeks to a daily maintenance dosage of 2.0 gm in divided doses. Maintenance therapy should be continued indefinitely, since long-term therapy with this drug has been shown to markedly reduce the relapse rate of ulcerative colitis.^{6,21} In one study, the relapse rate was reduced from 72% in control patients on placebo to 21% in treated patients.²¹ After one or two symptom-free years, discontinuation of the drug may be attempted in patients with mild disease; however, more prolonged therapy is advised in patients with moderate or severe colitis in remission, since discontinuation of the drug following one year of remission has been associated with a four-fold increase in the relapse rate.²²

The mechanism of action of sulfasalazine is unknown, but some information is available concerning its pharmacokinetics. Sulfasalazine is absorbed intact in the proximal small intestine and excreted in

*Sulfasalazine is the new official name for the drug that was formerly known as salicylazosulfapyridine.

the bile and is thereby cycled in the enterohepatic circulation. Most of the drug eventually passes into the colon, where metabolism by intestinal bacteria occurs, resulting in a reduction of the azo bond and cleavage of the molecule into its two constituents, 5-aminosalicylate and sulfapyridine.²³⁻²⁵ 5-Aminosalicylate remains in the colon and is excreted in the feces (its acetylated derivative, N-acetyl-5-aminosalicylate, may be recovered in urine). An early study described the capacity of sulfasalazine and 5-aminosalicylate to bind to connective tissue,²⁶ but whether this property is therapeutic remains speculative.²⁷ Sulfapyridine, by contrast, is absorbed and can be measured in the blood and recovered in the urine. It is this moiety of the parent molecule that probably is associated with many of the idiosyncratic reactions to the drug,²⁰ as well as with its toxic side effects.

Theoretically, the components of sulfasalazine could act therapeutically either as an anti-inflammatory agent (e.g., 5-aminosalicylate) or an antibacterial agent (e.g., sulfapyridine). However, no studies on the anti-inflammatory action of 5-aminosalicylate have been reported, and although sulfasalazine has been shown to alter intestinal flora,²⁸ no definite conclusions can be drawn concerning the therapeutic role of this activity in ulcerative colitis at this time.²⁹

Failure to respond to sulfasalazine after an adequate trial of several weeks is an indication to add topical corticosteroid therapy if the disease is limited to the rectosigmoid. Hydrocortisone (Cortenema®), hydrocortisone acetate (Cortifoam®) or methylprednisolone acetate (Medrol Enpak®) retention enemas are available for use. The usual dose per application is either 100 mg of hydrocortisone, 90 mg of hydrocortisone acetate, or 40 mg of methylprednisolone acetate, and the daily recommended dosage is one or two retention enemas daily for several weeks, tapering gradually to one application every other day for maintenance therapy until the patient is asymptomatic. Sulfasalazine should be continued during and after therapy with rectal steroids. The great majority of patients with mild disease limited to the distal colon will respond favorably to this combination therapy. If sulfasalazine cannot be given for any reason, steroid enema treatment can be used as the only form of therapy, since it has been shown to be effective in the treatment of acute attacks.³⁰ Patients with mild but more extensive disease involving the proximal colon are less likely to respond to topical steroids and may require oral steroids if sulfasalazine is not effective.

The beneficial effect of steroid enemas is thought to be a result of the local anti-inflammatory effect of steroids on the colonic and rectal mucosa. Although a percentage of the dose of rectal steroids is probably absorbed systemically, as evidenced by mild adrenal suppression, the major side effects of systemic steroid therapy are rarely observed with this

form of therapy. Occasionally, a short course of systemic corticosteroids (see below) is indicated when sulfasalazine and steroid enemas are ineffective in patients with disease limited to the rectosigmoid.

Marked emotional stress, anxiety, or depression may blunt the effectiveness of any pharmacotherapy in ulcerative colitis, and proper attentiveness to the psychological needs of each patient may prove extremely important in successful therapy. Therefore, a meaningful, on-going, physician-patient relationship is often crucial in the treatment of ulcerative colitis, regardless of its severity. Mild tranquilizers and sedatives may often prove beneficial. If there is an overriding anxiety or depression, psychiatric evaluation, supportive psychotherapy, and, occasionally, antidepressant therapy is indicated.^{31,32}

Moderate Disease. The initial approach to this group of patients is the same as that outlined above for mild disease, especially in patients with disease limited to the rectosigmoid or left colon. In addition, restrictions in diet to rest the bowel are recommended. Since there is some degree of constitutional symptomatology, hospitalization and complete bowel rest with intravenous fluids is occasionally warranted in these patients, allowing for gradual progression from a clear liquid diet to low residue diet as improvement occurs. This is especially indicated in patients with anorexia, weight loss, and postprandial abdominal cramps and diarrhea.

If the initial treatment with sulfasalazine and rectal steroids is ineffective after one or two weeks, or if the patient has universal colitis, the use of systemic corticosteroids is justified. The use of oral corticosteroids is reasonable in this group of patients, since most of them will be on some type of oral nutrition. Prednisone in high initial dosage of 40-60 mg per day in three divided doses is recommended, with slow tapering of the drug over many weeks or months once remission occurs. Antacids should be given regularly (15-30 cc of aluminum-magnesium hydroxide one and three hours following meals) during high dose steroid therapy to prevent gastritis. To minimize adrenal suppression and other side effects during the tapering period, the afternoon and evening doses can be reduced and withdrawn first so that when the total daily dose has been reduced to 20-30 mg, the entire amount may be given as one dose in the morning. This schedule conforms closely to the known peak output of steroids by the adrenal gland in man under normal conditions and therefore may be a more physiological way to give prednisone. Alternate day steroid maintenance therapy has also been advocated to reduce side effects, but many patients with colitis experience symptoms between such widely separated doses, and therefore, this form of therapy has not been generally accepted. If not already prescribed, sulfasalazine (2-4 gm daily) should be given

before tapering prednisone and continued indefinitely to prevent relapses. Systemic steroids and steroid enemas, alone or in combination, have been shown to be more effective than sulfasalazine in the therapy of acute attacks of ulcerative colitis³³ but are less effective in preventing recurrences.⁹

Finally, if oral steroids are ineffective, parenteral corticosteroids should be administered (see below).

Severe Disease. Patients presenting with a severe attack of ulcerative colitis definitely require hospitalization, bed rest, cessation of all oral intake, intravenous fluid and electrolyte replacement, and parenteral corticosteroids. Blood cultures should be obtained, and a course of broad-spectrum antibiotics should be initiated early in any patient suspected of having sepsis (high fever and marked leukocytosis). Washed, packed red blood cells and albumin transfusions should be given to maintain the hematocrit near 35% and the serum albumin above 3.5 gm%, respectively. Frequent abdominal examinations and plain X-rays of the abdomen are necessary to rule out perforation and toxic megacolon.

Parenteral corticosteroids may be given either as hydrocortisone sodium succinate (Solu-Cortef®) or as methylprednisolone sodium succinate (Solu-Medrol®). The usual recommended initial daily dose of hydrocortisone sodium succinate is 100 mg IV every 8 hours, and of methylprednisolone sodium succinate is 16-20 mg IV every 8 hours. Antacids should be given regularly (15-30 cc of aluminum-magnesium hydroxide every 2 hours) to prevent gastric erosions or peptic ulcer. As the patient's clinical status improves, the dose of steroids may be gradually reduced, clear liquids may be given by mouth, and if tolerated, the gradual introduction of bland, low residue foods may be attempted. Once oral feedings are well tolerated, intravenous fluids can be discontinued and oral corticosteroid (prednisone, prednisolone, or methylprednisolone) can be substituted for parenteral corticosteroid in equivalent dosage.

The effect of intravenous ACTH (corticotropin) is thought by some physicians to be superior to parenteral corticosteroids in the treatment of severe colitis and toxic megacolon. This impression is subjective for the most part. A study comparing the two drugs was reported in 1959, in which ACTH was compared to oral cortisone and was found to be slightly more effective in the treatment of acute attacks.⁸ A more recent report found no difference between intravenous ACTH and hydrocortisone in the treatment of acute colitis, but patients with Crohn's disease were included and not evaluated separately.³⁴ The recommended dose of ACTH is 40 units intravenously every 8-12 hours. Once remission has occurred, it is advised that ACTH be discontinued and oral corticosteroids be given for the duration of treatment, since the side effects of ACTH are more severe than those of oral steroids.⁸

If patients with severe disease fail to respond in

several weeks to parenteral ACTH or corticosteroids with persistent fever, anorexia, weight loss, bloody diarrhea, and abdominal tenderness, a decision to perform total proctocolectomy and permanent ileostomy must be seriously considered. Also, patients who only partially respond to steroid therapy and require relatively high maintenance therapy of corticosteroids or who have frequent relapses of moderate or severe disease should be considered for total proctocolectomy and ileostomy. Removal of the colon is curative, without risk of recurrence of disease in the small intestine.

There are many major side effects and complications of steroid therapy which may require specific treatment and either a reduction in or discontinuance of corticosteroids. These include acute psychosis, acute ulceration of stomach with massive gastrointestinal bleeding, infection, worsening of diabetes, hypertension, seizure disorders, osteoporosis, glaucoma, cataracts, thromboembolism, and myopathy. The presence of any of the above conditions prior to steroid therapy represents a relative contraindication to their use and may result in an earlier decision to perform proctocolectomy and ileostomy in a given patient with moderate or severe ulcerative colitis.

The development of toxic megacolon is a medical emergency and requires immediate attention, including nasogastric suction and the administration of broad-spectrum antibiotics and high doses of parenteral ACTH or corticosteroids; the patient should be observed extremely closely for impending perforation with frequent plain abdominal X-rays and careful abdominal examinations; incriminating drugs such as narcotics, anticholinergics and certain sedatives with muscle relaxant properties (e.g., diazepam) should be searched for in the medication record and discontinued. Barium enema is contraindicated. Correction of hypokalemia is critical. If there has been no improvement within 48-72 hours, early colectomy and ileostomy is probably warranted, since the mortality rate associated with toxic megacolon is extremely high.³⁵

In recent years both oral elemental diets and total parenteral nutrition (hyperalimentation) have become available to reverse the catabolic state that is so prevalent in patients with moderate and severe ulcerative colitis, providing high caloric and protein intake while maintaining adequate bowel rest. It is especially indicated in any patient with severe disease and progressive weight loss in whom regular oral feedings are not well tolerated. Since parenteral hyperalimentation is associated with serious complications, oral hyperalimentation should be attempted first. Oral elemental diets with minimal or no residue are now available and are relatively well tolerated by patients with ulcerative colitis. They can supply up to 3,000 calories and 125 gms of protein per day in the form of amino acids, casein, or egg albumin (e.g., Vivonex® High Nitrogen, Precision High Nitrogen,® Flexical®). A small pediatric

nasogastric feeding tube may prove helpful in administering the liquid elemental diet in patients who cannot tolerate the taste of these preparations. It is important to introduce elemental diets in more dilute and limited servings and gradually increase the osmolality and volume of the diet in order to prevent diarrhea caused by a high osmotic load. If a patient cannot tolerate elemental diets because of persistent diarrhea, parenteral nutrition may then be indicated.

The use of azathioprine (Imuran®) in ulcerative colitis is currently under investigation. Although several initial reports have been favorable, no controlled studies have yet appeared in the literature supporting the effectiveness of azathioprine in ulcerative colitis. A recent study in patients with chronic ulcerative colitis on maintenance corticosteroid therapy did demonstrate a beneficial effect of azathioprine in permitting a reduction in steroid dosage but failed to show a dramatic effect in relieving symptoms.³⁶ Recommendations for the use of azathioprine in ulcerative colitis must therefore await further evaluation.

Crohn's Disease

Since Crohn's disease is a chronic disease with a wide variety of clinical presentations, depending upon the sites and extent of involvement and the number and location of complications, such as fistulae, pericolic abscesses and strictures, the management is often complex, and the treatment must, therefore, be individualized. Although pharmacotherapy is not as frequently associated with such dramatic responses as are so often seen in ulcerative colitis, drug treatment is successful in relieving the symptoms of active inflammation, such as fever, abdominal pain, and watery diarrhea in many patients with Crohn's disease, whether it be ileitis, colitis, or ileocolitis.

Patients with symptomatic Crohn's disease who do not have fistulae or pericolic abscesses should undergo the same basic therapeutic trials that were outlined under treatment of ulcerative colitis. A trial of sulfasalazine is recommended in patients with mild Crohn's disease. A recent controlled study reported significant improvement in the symptoms of Crohn's ileitis in patients treated with sulfasalazine,³⁷ confirming earlier clinical impressions of its effectiveness.

Patients with moderate or severe symptoms, including anorexia, weight loss, profuse diarrhea, and abdominal pain, are candidates for corticosteroid therapy, either oral or parenteral, depending upon the clinical status. In addition, hospitalization and bowel rest are often indicated, and symptomatic relief of abdominal cramps and diarrhea can be afforded by the judicious use of opiates (Lomotil®, Deodorized Tincture of Opium®), anticholinergic drugs, and sedation. There are no controlled clinical studies of the use of corticosteroids in Crohn's disease comparable to those reported in ulcerative co-

litis, but many patients appear to respond to steroid therapy with a decrease in symptoms.

It is the author's personal opinion from recent experience that a short course of azathioprine (Imuran) in low dosage (50-100 mg daily in adults) is frequently beneficial in patients who fail to respond to sulfasalazine and corticosteroid therapy. Oral corticosteroids are usually continued in low dosage (e.g., prednisone, 10-20 mg daily), concomitant with azathioprine therapy. Azathioprine, however, should not be used in patients with sepsis, such as intra-abdominal abscess, or in patients who are likely to require surgical intervention in the immediate future.

Initial uncontrolled reports of the use of azathioprine in Crohn's disease were encouraging, especially in its apparent effect in accelerating the healing of enterocutaneous fistulae.^{38,39,40} However, three controlled studies have since appeared in the literature, two of which failed to demonstrate a significant effect in inducing remissions.^{41,42} The third study reported that azathioprine was beneficial in maintaining remissions in Crohn's disease.⁴³ A National Cooperative Crohn's Disease Study is currently in progress comparing the effectiveness of placebo, sulfasalazine, corticosteroids, and azathioprine in this disease.

Azathioprine is absorbed by the small intestine and metabolized to 6-mercaptopurine, which in turn is further catabolized to various oxidized and methylated derivatives. Its pharmacologic effect is based upon its activity as a purine analog, thereby blocking the interconversion of nucleotides and impairing the synthesis of nucleic acids. Its primary action is immunosuppression, both by interfering with the induction of humoral antibody production⁴⁴ and by inhibiting cellular immunity.⁴⁵ It is questionable, however, whether azathioprine is immunosuppressive in the low dosages used in inflammatory bowel disease. Like other immunosuppressives, azathioprine also acts as an anti-inflammatory agent.⁴⁶ Its potential value and mode of action in inflammatory bowel disease needs further elucidation.

The most serious side effect of azathioprine is severe and irreversible bone marrow depression. Frequent complete blood counts including platelet counts should be ordered during the initial one to two weeks of therapy and weekly thereafter. The drug should be discontinued or the dosage reduced if leukopenia or thrombocytopenia occur. Other side effects include nausea and vomiting, drug fever, skin rash, and occasional hepatic dysfunction.

The use of oral elemental diets and total parenteral nutrition in Crohn's disease is currently being evaluated. As discussed previously, these measures are indicated in any seriously ill patient with progressive weight loss who requires prolonged bowel rest. Total parenteral nutrition may reverse a deteriorating clinical course and allow additional time

for a patient to respond to treatment, thus avoiding surgical intervention.

As emphasized above in the treatment of ulcerative colitis, successful management of Crohn's disease also requires an appreciation of the patient's psychological needs and problems. Severe emotional stress, anxiety, and depression may seriously interfere with the patient's clinical response to therapy. A strong physician-patient relationship is extremely important, and psychiatric evaluation, supportive psychotherapy, and at times, antidepressant therapy are often indicated early in the course of treatment.

The indications for surgery in Crohn's disease include the presence of complications, such as fistulae, intra-abdominal abscesses and intestinal obstruction, and the failure to respond to conservative management. The tendency for Crohn's disease to recur postoperatively⁴⁷ has led to an appropriate reluctance to perform surgery, especially in patients with regional ileitis. However, the presence of intra-abdominal sepsis and fistulae do require surgical intervention. Furthermore, patients with severe Crohn's colitis or ileocolitis who do not respond to intensive medical management over a period of several weeks (persistent fever, diarrhea, anorexia, weight loss, anemia and hypoalbuminemia) should seriously be considered for colectomy or ileocelectomy, since many patients do remarkably well following resection of diseased bowel.¹⁸ Further delay in surgery after all attempts to produce a remission have failed is, in the author's opinion, unjustified and will result in greater surgical risk at a later date. However, the presence of diffuse disease, extensive involvement of the small intestine, complicated internal fistulae and intra-abdominal abscesses do pose special and difficult problems that require skilled and experienced surgical management. Surgery in such situations is often of only limited benefit, and the postoperative recurrence rate is high.

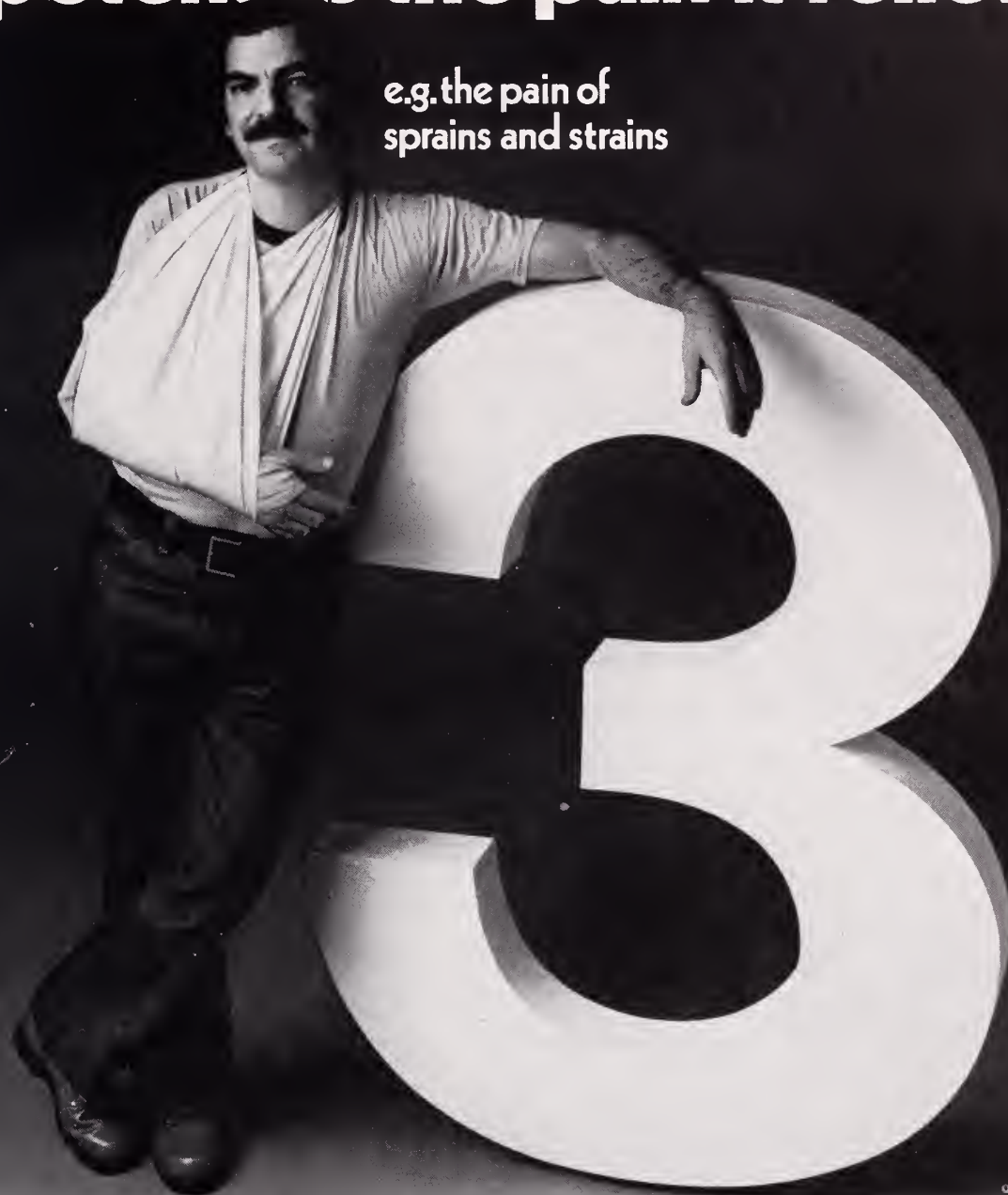
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Honorary Pin Recipients Receive Awards at 1976 Annual Session of the M.M.A.

Presentation of the Association's Honorary Pins was made by Euclid M. Hanbury, Jr., M.D., President of the M.M.A., at the Annual Banquet, Monday evening, June 7 at 7:00 P.M.

FIFTY-YEAR PINS

Fifty-Year Lapel Pins were presented to the following members who were graduated from Medical School in 1926:

Androscoggin County

CARLETON H. RAND, M.D. — Dr. Rand, born in Lewiston, Maine, was graduated from Bates College and received his medical degree from Tufts University School of Medicine in 1926. He interned at the Central Maine General Hospital in Lewiston. An orthopedic surgeon, Dr. Rand started his practice in Lewiston in 1927 and is on the Surgical Staff at the Central Maine General Hospital.

Cumberland County

OSCAR R. JOHNSON, M.D. — Born in Monson, Maine, Dr. Johnson was graduated from the University of Maine, attended Colby College for one year, and received his medical degree from Yale University School of Medicine in 1926. He interned at the Maine Medical Center in Portland and served a residency in dermatology at the Massachusetts General Hospital. Dr. Johnson started his practice in Westbrook in 1927 and located in Portland in 1931 where he was affiliated with the Children's Hospital, the Maine Eye and Ear Infirmary and the Maine Medical Center until his retirement. He is a Life Member of the American Academy of Dermatology.

Kennebec County

FRANK B. BULL, M.D. — Dr. Bull, born in Brampton, Ontario, received his medical degree from the University of Toronto Faculty of Medicine in 1926. He interned at the Toronto Western Hospital and served a residency in surgery at the Lincoln Hospital in New York. A general surgeon, Dr. Bull practiced in Sharon, Connecticut and Cambridge, New York, locating in Gardiner, Maine in 1930. During World War II, he served in the U.S. Army as a Lieutenant Colonel.

MATTHIAS MARQUARDT, M.D. — A native of Rietheim-Tuttlingen, Germany, Dr. Marquardt attended schools in Germany and received his medical degree from Chicago Medical School University of Health Sciences in 1926. He took postgraduate courses at the Children's Memorial Hospital in Chicago and the Waterbury Hospital in Connecticut. Dr. Marquardt located in Augusta, Maine in 1926 where he practiced at the Augusta State Hospital until his retirement.

M. TIECHE SHELTON, M.D. — Dr. Shelton, a native of Chatham, Virginia, was graduated from Duke University in 1922 and received his medical degree from Johns Hopkins University Medical College in 1926. He interned at the Church Home & Infirmary in Baltimore, Maryland and served residencies at St. Mary's Hospital in Pierre, South Dakota, Yale University and the Yale-New Haven Hospital. A general surgeon and family practitioner, Dr. Shelton practiced in Los Angeles and Harrisonburg, Virginia, locating in Augusta, Maine in 1934. He is affiliated with the Augusta General Hospital and Veterans Administration Center at Togus. Dr. Shelton served in the U.S. Army Medical Corps from 1942 to 1946 and retired from the U.S. Army Reserves as a Lieutenant Colonel in 1951.

Penobscot County

CARL E. BLAISDELL, M.D. — Born in North Sullivan, Maine, Dr. Blaisdell was graduated from the University of Maine and received his medical degree from Tufts University School of Medicine in 1926. He took a postgraduate course at the Eastern Maine General Hospital in Bangor, Maine. A urologist, Dr. Blaisdell located in Bangor in 1927.

FIFTY-FIVE-YEAR PINS

A Fifty-Five-Year Pin was presented to the following member who received a Fifty-Year Pin in 1971:

Cumberland County

EDWARD BLUMBERG, M.D. — Dr. Blumberg, a native of Leipzig, Germany, received his medical degree from the University of Leipzig Faculty of Medicine, Saxony in 1921 and interned at Clinics at that University from 1921 to 1923. He specialized in Mental Deficiencies and was on the staff at Pineland Hospital and Training Center in Pownal, Maine from 1955 to 1965 when he moved to Brooklyn, New York where he now resides.

SIXTY-YEAR PINS

Sixty-Year Pins were presented to the following members who received Fifty-Year Pins in 1966:

Cumberland County

GEORGE O. CUMMINGS, SR., M.D. — Dr. Cummings, a native of Portland, Maine, was graduated from Bowdoin College in 1913 and received his medical degree from Bowdoin Medical School in 1916. He interned at the Maine General Hospital from 1916 to 1917, attended the Graduate School of Medicine of the University of Pennsylvania from 1922 to 1923, following which he returned to Portland where he limited his practice to the disease of the ears, nose and throat. Dr. Cum-



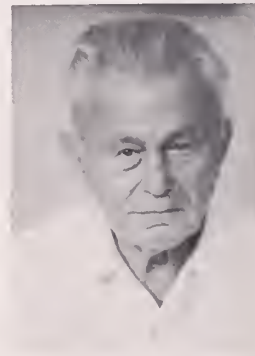
Dr. Johnson



Dr. Bull



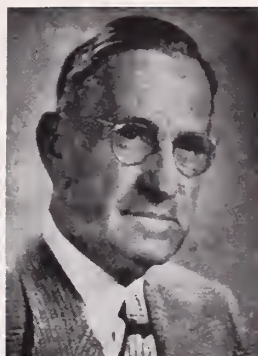
Dr. Shelton



Dr. Blumberg



Dr. Cummings



Dr. Wyman

mings, a diplomate of the Board of Otolaryngology, is a member of several national medical organizations. During World War I, he served in the U.S. Navy from 1917 to 1919 as a Lieutenant.

HERMAN C. PETTERSON, M.D. — Dr. Petterson, a family practitioner at Chebeague Island, Maine, is a native of Chicago, Illinois. He attended schools in Naperville, Illinois and received his medical degree from Hahnemann Medical College in 1916. He interned at the New York City Hospital and the Massachusetts Memorial Hospital from 1916 to 1917 and took postgraduate courses at Harvard Medical School in 1920. Dr. Petterson practiced in Boston from 1921 to 1953, during which time he was Chief of Pediatrics at the Massachusetts Memorial Hospital from 1931 to 1953, the St. Mar-

garet Hospital from 1946 to 1953 and the Massachusetts General Hospital from 1933 to 1953.

SIXTY-FIVE-YEAR PINS

Sixty-Five-Year Pins were presented to the following members who received Fifty-Year Pins in 1961:

Knox County

FRED G. CAMPBELL, M.D. — A family practitioner in Warren, Maine since 1913, Dr. Campbell is a native of Rockland, Maine. He attended the University of Maine in Orono and received his medical degree from Baltimore Medical College in 1911. He interned at the Worcester State Hospital in Massachusetts.

Piscataquis County

EDWIN T. WYMAN, M.D. — Born in Sebec, Maine, Dr. Wyman retired from the practice of pediatrics in Boston in 1969 and returned to Sebec where he now resides. He attended Higgins Classical Institute and received his medical degree from Tufts University School of Medicine in 1911. He interned at the Mt. Auburn Hospital in Cambridge, Massachusetts from 1912 to 1913 and was a resident at the Children's Hospital in Boston from 1914 to 1915. Dr. Wyman was in the pediatric service at the Children's Hospital, Boston, the Mt. Auburn Hospital, Cambridge and the Boston Lying-In Hospital from 1914 until 1969 and is at present Physician Emeritus at the Children's Hospital Medical Center in Boston. He was for many years instructor in the Department of Pediatrics at Harvard Medical School. During World War I, he served in the U.S. Army Medical Corps and was discharged as a Major.

DRUG THERAPY REVIEWS — PHARMACOTHERAPY OF INFLAMMATORY BOWEL DISEASE

Continued from Page 214

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Reminder to M.M.A. Members

CONTINUING MEDICAL EDUCATION ACTIVITY REPORT

The bylaws of the Maine Medical Association were amended in June of 1973 as follows: Chapter I, Section 11, — "Each member of the Maine Medical Association shall be required to report his activities in continuing medical education every year according to a format provided by the Committee on Continuing Medical Education."

Only active, dues-paying members are required to report this year.

Please fill in your activity report promptly and return to the M.M.A. office, P.O. Box 250, Brunswick, Maine 04011.



Maine Blue Cross and Blue Shield News

HEALTH INFORMATION PROGRAM LAUNCHED

"Update on Health," a nationally syndicated series designed to inform Americans about health care, premiered in Maine July 5th under the auspices of Maine Blue Cross and Blue Shield.

The multi-faceted program includes: "Update on Health," 156 thrice weekly, 1½ minute health information reports; "Housecall," a weekly half-hour series on health care involving interviews with medical experts and viewer letters; and four 60-minute specials on breast cancer, heart disease, nutrition and child rearing.

The 1½ minute information spots run Monday, Wednesday, and Friday evenings between 6:58 and 7:00 on Channel 13 in Portland and Channel 2 in Bangor. The half-hour program runs every Monday on the same channels from 1 to 1:30 in the afternoon.

Two of the hour specials have already been shown in Maine to determine viewer response to the format. Both the specials on heart disease and nutrition received very positive consumer and provider response. During the week following the heart special, a number of people wrote or called indicating that they had altered their smoking, exercise, or eating habits to effect a healthier lifestyle.

Timothy Johnson, M. D., is moderator of all three "Update" segments. He is Director of Lay Health Information at Harvard University School of Medicine, author of *What You Should Know About Health Care Before You Call A Physician* (McGraw-Hill, 1975), and he holds joint clinical instructor positions in medicine at Harvard and Massachusetts General Hospital.

The basic reason Maine Blue Cross and Blue Shield has positioned itself so prominently in mass public health information is to help the consumer develop the knowledge with which he or she can take responsibility for his or her own health. The "Update" series does not turn the viewer into an instant diagnostician, but will provide the individual with the means to evaluate his or her own lifestyle against specific health norms.

"The programs are designed to develop better informed health care consumers," said Dr. Johnson in explaining his involvement in health information. "In order to aid improvements in health in this country in the next ten years, we as health practitioners, educators, and communicators must first change the prevailing attitude of the American public toward medicine. That attitude generally disregards preventive self-care and minimizes the decision-making each of us must do for ourselves in choosing and evaluating medical care."

"Important as are researchers, government agencies, and physicians themselves, their impact is probably less significant than the help each health care consumer can provide himself."

County Society Notes

Kennebec

The Kennebec County Medical Association met at the Holiday Inn in Augusta, Maine on March 18, 1976, with 35 members and 3 guests present. The meeting was called to order by the President, Dr. James C. Hayes, at 8:03 p.m.

The minutes of the previous meeting were read and accepted.

Letters from the Maine Medical Association honoring Drs. Matthias Marquardt, Frank Bull and M. Tische Shelton for fifty years of practice were read.

New business: The applications for membership of Drs. Joseph M. Mann, III, C. Dalton Jagh and B. Lincoln Wales were read.

Old business: Application of Dr. Romulo Beltran was voted on favorably and he is welcomed into membership in the Association. The bylaws which had been placed upon the table at the previous meeting were voted on and accepted, replacing the previous bylaws of the Association.

Dr. Hayes then introduced Ms. Laura Franciose of Maine Blue Cross and Blue Shield who spoke briefly and then introduced Mr. Thomas Cathcart, who spoke to the members of the Association about various aspects of Maine's Blue Cross and Blue Shield program. A lively discussion of various aspects of third-party reimbursements followed and the membership enjoyed the discussion greatly. Meeting closed at 9:15 p.m.

The Kennebec County Medical Association met at the Silent Woman Restaurant in Waterville, Maine on April 15, 1976, with thirty-two members and one guest present. The meeting was called to order by the President, Dr. James C. Hayes, at 8:05 p.m.

Minutes of the previous meeting were read and accepted.

Letters were read from Mrs. DeWitt of the Department of Human Services and Mr. Cathcart and Ms. Laura Franciose of Blue Cross and Blue Shield. Dr. Chamberlin reported briefly on the recent meeting of the House of Delegates and read the resolutions so that the members would know what was being considered for resolutions. A motion was made by Dr. Howard H. Milliken to discuss these resolutions at this time, but this motion was defeated. A second motion was made by Dr. Richard E. Barron that the resolutions be distributed to all of the members along with a ballot so that they could indicate their support or lack of it, of the resolutions for instructional purposes for the delegates and that this be completed prior to the next meeting of the Council and this motion was passed.

There was no new business.

Old business: The applications of Drs. Joseph M. Mann, III, B. Lincoln Wales and C. Dalton Jagh were favorably acted upon and they are welcomed into the Association. The Nominating Committee presented its nomination for the vacancy on the Council as Dr. Gareth O. M. Jones of Augusta, and he was elected.

Dr. Hayes introduced the speaker for the evening, Dr. Francis I. Kittredge, who presented to the members of the Association the deliberations of the Maine Malpractice Commission in a most informative way and discussion was held which indicated that the members had completely enjoyed Dr. Kittredge's presentation.

O. THOMAS FEAGIN, M.D., *Secretary*

Androscoggin

The monthly meeting of the Androscoggin County Medical Association was held jointly with the area pharmacists at Steckino's Restaurant in Lewiston, Maine on April 22, 1976.

The business meeting was called to order by the President, Dr. Stanley D. Rosenblatt, at 8:10 p.m., with 20 members present and ten guests.

Minutes of the March meeting were accepted as read.

Correspondence was read by the Secretary.

Dr. Thomas F. Shields reported on the interim meeting of the House of Delegates held at Bangor on April 3, 1976.

Optometrists' Petition signed by physicians was commented on.

The Resolutions presented were listed. The one on Continuing Medical Education elicited the most discussion.

Dr. Richard T. Chamberlin has been appointed Assistant Executive Director of the Maine Medical Association.

Budget of M.M.A. was discussed.

Slate for Representative to Executive Committee was presented and voted upon. Dr. Cyprien L. Martel, Jr. was elected.

Dr. Charles A. Hannigan introduced the members of the Panel. Substitution law was discussed. Question and answer period regarding problems encountered followed.

The meeting adjourned at 10:15 p.m.

DONALD L. ANDERSON, M.D., *Secretary Pro Tem*

Lincoln-Sagadahoc

The regular monthly meeting of the Lincoln-Sagadahoc County Medical Society was held on April 20, 1976 at the Ledges Inn in Wiscasset, Maine. There were twenty-three members and guests present.

The meeting was called to order at 8:36 p.m. by the President, Dr. David S. Hill, who introduced Mr. Wes Nichols of the Kno-Wal-Lin Home Health Agency and Mr. Robert Liversidge of the Bath-Brunswick agency. These agency directors spoke about the organization and functions of home health agencies, as well as methods of finance. A great deal of discussion was elicited.

The Secretary at 9:28 p.m. read the minutes of the last meeting, which were accepted as read.

The Secretary read a letter from Dr. Paul A. Fichtner, announcing his retirement from active practice. Dr. Richard C. Leck moved and Dr. Francis A. Winchenbach seconded the motion that Dr. Fichtner be recommended for affiliate membership.

Dr. Anthony J. Horstman asked for direction from the members regarding four proposed resolutions to come before the House of Delegates in June. The first was a proposal for unified State and county society membership. A show of hands favored opposition to this proposed resolution. The next resolution would require that any member suspended for nonpayment of dues satisfy all debts to the Association before reinstatement. The members supported this principle. The next proposed resolution would require members to obtain 150 hours of postgraduate medical education every three years in order to maintain Association membership. The straw vote was against adoption. The next proposal would direct the M.M.A. to attempt to obtain the right of a physician to bill directly to Medicaid patients or take assignment under Medicaid, the same choice as under Medicare. The straw vote favored adoption.

Dr. Leck then spoke on the April meeting of the House of Delegates. Health insurance rates for the M.M.A. Blue Cross/Blue Shield policy will not change this year. All skilled nursing facilities will need medical directors. The M.M.A. has hired an Assistant to the Executive Director. PSRO is preparing to conduct medical audit in physicians' offices. A medical central information bank is proposed by the Department of Human Services. Blue Shield has the power to discount physicians' fees unilaterally, and some impetus has been developed to deny this right because of decreased medical representation on the Blue board. Dr. Winchenbach also discussed this subject. A Swine Influenza chairman will be chosen at the May meeting.

The regular monthly meeting of the Lincoln-Sagadahoc County Medical Society was held at The Ledges Inn, Wiscasset, Tuesday, May 18, 1976.

There were twenty-nine members and guests present. The secretary, after dinner, introduced Mr. Richard King, of the Bath-Brunswick Mental Health Agency, who spoke on the history and functions of the Agency.

The minutes of the April meeting were read and accepted as read. The secretary then asked for old business; Dr. Elihu York was appointed Swine Flu chairman.

The new business consisted of discussion of a letter from Dr. John F. Dougherty announcing his retirement from practice the first of April. The motion was made, seconded, and unanimously passed, that Dr. Dougherty's name be recommended for Affiliate membership.

The meeting was then adjourned.

GEORGE W. BOSTWICK, M.D., *Secretary*

Penobscot

The monthly meeting of the Penobscot County Medical Society was held on March 16, 1976 at the Helm Restaurant in Bangor, Maine.

The meeting was opened by the President, Dr. Thornton W. Merriam, Jr. and the minutes of the previous meeting were read and approved.

President Merriam made the following announcements. The House of Delegates of the Maine Medical Association will meet

at the Eastern Maine Medical Center on April 3, 1976. The Pine Tree Organization for Professional Standards Review has requested volunteers to serve on a committee to review the utilization of services within nursing homes. Finally, it was announced that the Bylaws are being reprinted and copies will be forthcoming to every member.

There were no communications nor old business.

Under new business, Dr. Lewis E. Phillips brought to our attention that the fee schedule utilized under the Veterans Administration appears to be different than that utilized by Medicare, and the reasons for this difference are not apparent. It would appear that some explanation for this difference would be appreciated.

The scientific portion of the meeting was presented by Dr. Francis I. Kittredge who headed a discussion regarding a Patient Injury Prevention Panel. This panel was intended to represent a possible solution to the very large question of medical malpractice. Numerous questions were then brought forward and discussed.

As there was no further business, the meeting was adjourned.

PHILIP G. HUNTER, M.D., *Secretary*

Letter to the Editor

To the Editor:

Again this year I am compiling a Biting Insect Summary and would appreciate any case reports of unusual allergic reactions, especially systemic (sneezing, wheezing, urticaria) to bites of insects; i.e., mosquitoes, fleas, gnats, kissing bugs, bedbugs, chiggers, black flies, horseflies, sandflies, deerflies, etc.

I would like physicians to supply me with case reports of those patients who have had unusual reactions to such insects. Include in your reports the type of reactions (immediate and delayed symptoms), treatment, the age, sex, and race of the patient, the

site of the bite(s), the season of the year, and any other associated allergies.

If skin tests and hyposensitization were instituted, I would like the report of both. Please note that it is the biting (not stinging) insect in which I am interested.

If you have found any insect repellent, local treatment, or insecticides of value, I would also appreciate this.

Please send this information to the following address:

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The Journal of the Maine Medical Association

Volume Sixty-seven

Brunswick, Maine, August 1976

Number 8

The Plaster Cast for Colles' Fracture

ARNOLD SOREN, M.D., D.O.S.*

Maintenance of proper alignment in Colles' fracture is difficult, even when reduction of the dorsal and radial displacement has been achieved relatively easily. Watson-Jones¹ has emphasized this difficulty. Therefore, the Cotton-Loder² technique immobilizes the wrist in marked volar flexion to prevent dorsal re-displacement. However, no force is exerted to prevent radial re-displacement. Moreover, after 6 weeks of immobilization in the Cotton-Loder position the dorsal tendons have undergone prolonged stretching, and require several months of functional treatment to recover active dorsiflexion.

On the other hand, the routine type of plaster cast secures the aligned fragments less reliably than the former method; it often becomes too wide subsequent to decreased swelling of the wrist; partial or complete re-dislocation may occur. This necessitates a second reduction and application of a new plaster cast, unless the displacement is accepted as permanent. Bacorn and Kurtzke³ reported healing with displacement in a significant percentage of patients treated for Colles' fracture. These authors noted in a series of 1,700 patients that 436 patients (25.6%) remained with mild deformity, 361 (21.2%) with moderate deformity, and 89 (5.2%) with marked deformity. Contrary to the common belief, the residual deformity was associated with a commensurate degree of disability.

Therefore, the following technique is recommended to secure proper reduction and fixation of the fragments while avoiding the drawbacks of the aforementioned methods.

With the patient in the supine position, the fracture site is infiltrated with 10-15 ml of $\frac{1}{2}$ to $\frac{3}{4}\%$ Procaine[®] solution. The elbow is placed in 90° flex-

ion and neutral rotation. Traction is exerted on the fingers and wrist, while counter-traction is exerted on the arm. The fragments are disengaged, and the distal fragment is aligned, by dorsal and radial pressure, with the proximal fragment. The wrist is then held in mid-position between pronation and supination, and between radial and ulnar deviation. Pronation of the wrist is not attempted, because the proximal fragment assumes neutral rotation by muscle action. Ulnar deviation is likewise avoided, because it causes ulnar tilting of the articular surface of the radius and radial protrusion at the fracture site.

While traction is maintained, a thin layer of sheet wadding is applied from the knuckles to above the elbow, and is fixed with a 5" circular plaster bandage. A plaster splint of 8 thicknesses is then applied on the dorso-radial aspect of the arm and hand. A circular plaster bandage completes the cast. Lukewarm water is used to slow the setting process of the plaster.

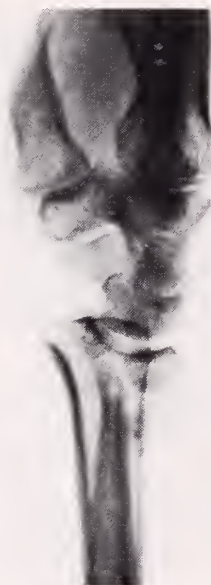
As the plaster cast begins to harden, gentle pressure is exerted with the volar aspects of the thumbs on the dorsal and radial sides of the cast directly over the distal fragment of the radius. Thus, when the plaster cast has set, two indentations (Fig. 1) have been formed which exert pressure on the distal radial fragment and serve to prevent re-displacement in two planes. Care must be taken to mold the indentations with smooth rotating motions of the thumbs in order to avoid corresponding sharp protrusions on the inner surface of the plaster cast. By distributing the pressure over relatively large surfaces, pressure sores are avoided. The traction on the fingers is continued until the plaster cast has hardened.

After satisfactory application of the plaster cast, the arm is kept elevated on two pillows, and is checked at regular intervals for adequacy of circulation. Suspension of the arm is advised for con-

*Associate Professor of Orthopaedic Surgery, New York University School of Medicine, 550 First Ave., New York, N.Y. 10016.



Fig. 1. Oblique view of plaster cast with a dorsal and a radial indentation.



Figs. 2, 3, and 4. Dorsal angulation in Colles' fracture; correction maintained by plaster cast with indentation; satisfactory healing.

fused or uncooperative patients. Under normal conditions, the pain is generalized, moderate, and not localized to the indented areas. If sharp pain does persist in these areas, the plaster cast must be changed. If the swelling of the hand increases, and the generalized pain becomes severe, the plaster cast and the sheet wadding are longitudinally split down to the skin; the edges of the plaster cast are spread.

The plaster cast is changed after 10 to 14 days, if it has become loose following decrease of the swelling of the wrist. However, snugness is usually experienced by the patient throughout the duration of immobilization due to the indentations in the plaster cast. X-ray examination on the tenth day should verify that with good reduction and a cor-

rectly applied plaster cast the fragments are maintained in accurate alignment. The patients are then instructed in active exercises of the fingers and shoulder. Since osseous union usually requires 6 weeks or more, the plaster cast is maintained for this period. After healing has been clinically and radiologically evidenced, active motion of the wrist and elbow joints is begun.

Utilizing this technique, accurate reduction and a circular plaster cast with dorsal and radial indentations, 162 patients with plaster cast were treated during the period between 1964 and 1974. The morphological, radiological (Figs. 2-7) and functional results were good in all but 4 patients. In the latter, elderly people, intolerance to the circular cast required use of only a dorsal plaster



Figs. 5, 6, and 7. Radial displacement in Colles' fracture; correction maintained by plaster cast with indentation; satisfactory healing.

splint; re-displacement with "step-off" deformity resulted in each case.

Satisfactory results were obtained by this method in 158 of 162 patients.

SUMMARY

Reduction of the distal fragment is often difficult to secure in the treatment of Colles' fracture. A circular plaster cast is utilized with two indentations molded over the distal fragment. These indentations prevent dorsal and/or radial displacement.

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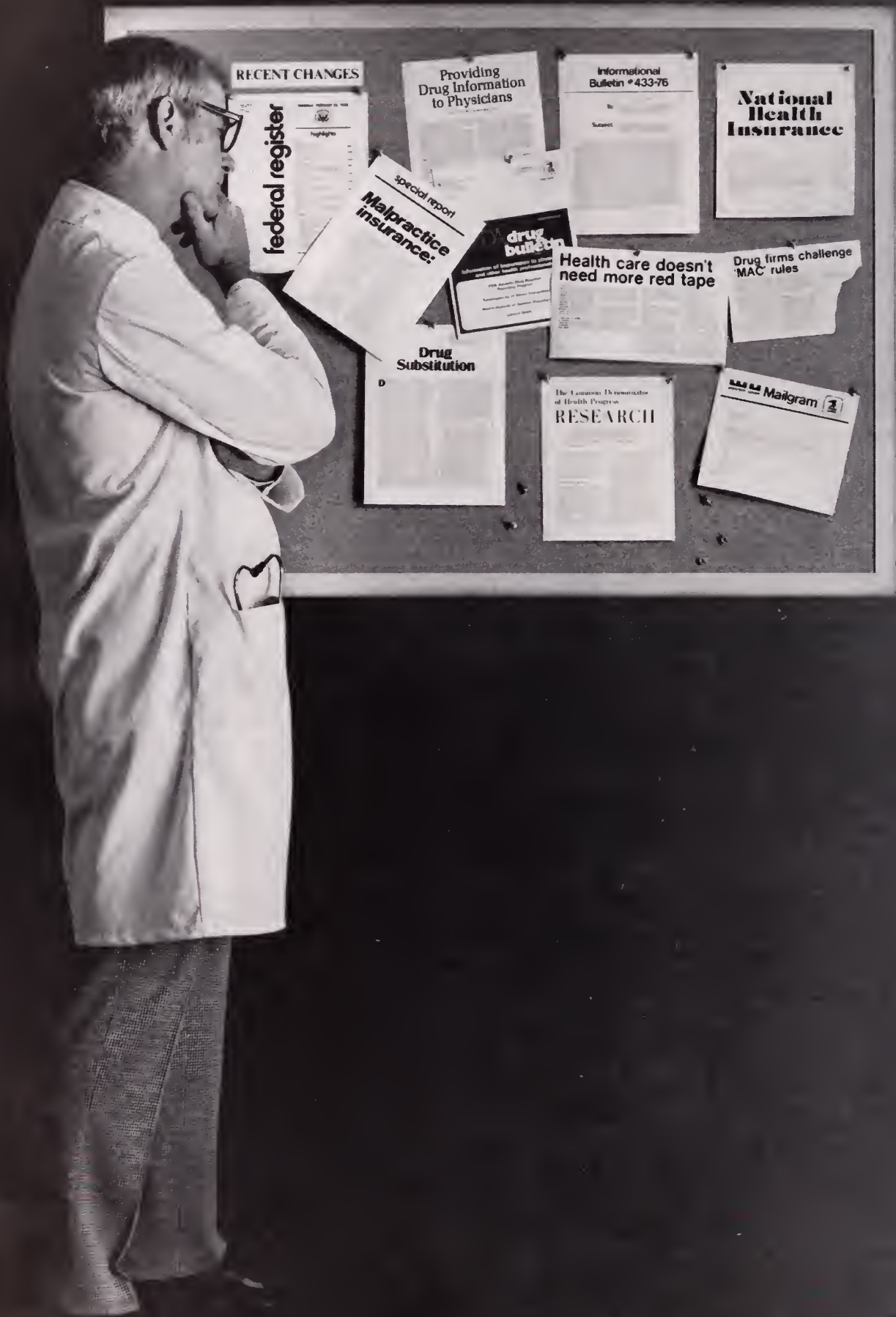
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Mailgram

THERE ARE A LOT OF PEOPLE GETTING BETWEEN YOU AND YOUR PATIENT.

Medicine today is in the spotlight, subjected to all kinds of scrutiny. Your control over patient therapy is being monitored, judged and occasionally abrogated, sometimes by unknown third parties.

The worry is that in the wake of this focus, the relationship between you and your patient will be weakened, without offsetting benefits. Consider three examples:

Drug substitution In most states, pharmacy laws, regulations or professional custom stipulate that your non-generic prescriptions be filled with the precise products you prescribe. But in the last five years, a dozen or more State laws have been changed, permitting the pharmacist in most cases to select a product of the same generic drug to fill any prescription.

Ironically, this dilution of physician control has taken place against a background of growing evidence that purportedly equivalent drug products may be inequivalent, since neither present drug standards nor their enforcement are optimal. In fact, the FDA itself says it has not enforced the same standards for hundreds of "follow-on" products that it had applied to the original NDA approvals. Thus physician control over patient therapy is being eroded with a risk that patients may be exposed to drugs of uncertain quality.

The major advertised claim for substitution is reduced prescription prices for consumers. Yet no documentation of any significant savings has been produced.

MAC Maximum Allowable Cost, MAC for short, is a Federal regulation designed to cut the Government's drug bill by setting price ceilings for drugs dispensed to Medicare and Medicaid patients. Unless the prescriber certifies on the prescription that a particular product is medically necessary, the Government intends to pay only for the cost of the lowest-priced, purportedly equivalent,

generally-available product. The effect of the program may be that elderly and indigent patients will be restricted to products which someone in Washington believes are priced right. Practicing doctors will have little to say about administration of the program, since Government will have absolute authority to make its choices stick.

The drug lag The future of drug and device research depends upon a scientific and regulatory environment that encourages therapeutic innovations. The American pharmaceutical industry annually is spending more than \$1 billion of its own funds and evaluating more than 1,200 investigational compounds in clinical research. Disease targets include cancer, atherosclerosis, viruses and central nervous system disorders, among others. But there is a major barrier to the flow of new drugs to your patients: The cost of the research is more than ten times what it was, per product, in 1962; and whereas governmental clearance of new drug applications took six months then, it commonly consumes two years now.

The FDA needs adequate time, of course, to consider data. But it is equally clear that the present approval process contributes to needless delay of needed therapy. That's why the increased efficiency of the drug approval process is vital to all our futures.

If these issues concern you, we suggest that you make your voice heard—among your colleagues and your representatives in State legislatures and in Washington.

It could make a difference in your practice tomorrow.

Pharmaceutical Manufacturers Association
1155 Fifteenth Street, N.W., Washington, D.C. 20005



Hypertensive Cerebellar Hemorrhage

FREDERICK M. VINCENT, M.D.*

In 1813 Sedillot of Paris reported the first case of a cerebellar hemorrhage, and 29 years later Huss of Sweden reported the second case.¹ Childs is the first American author (1858). His case was that of a girl whose symptoms developed while amusing a child by violently shaking her head.¹ The first report of a successful operation for a cerebellar hemorrhage was made by Ballance in 1906.² It is evident from the past literature that cerebellar hemorrhage has been felt to be relatively rare when compared to other intracranial hemorrhages, and many isolated reports have followed in the literature. A number of large post-mortem series have found the incidence of cerebellar hemorrhage to range from 9.0 to 13.0%, with the average incidence approximately 10.0%.^{3,4} It was evident from these studies that the diagnosis was all too commonly made at post-mortem examination. Thus, far from being a rarity, cerebellar hemorrhage accounts for approximately 10% of all intracranial intraparenchymal bleeds.^{3,5}

The purpose of this paper is to present the case report of a patient who expired from a cerebellar hemorrhage that was diagnosed at necropsy and to review the recent literature on cerebellar hemorrhage and to call to attention certain symptoms and signs that may indicate the presence of a cerebellar hemorrhage.

CASE REPORT

A 74-year-old female was admitted to the hospital in coma. She had been in prior good health except for intermittent hypertension. The patient was non-responsive to verbal or tactile stimuli. The blood pressure was 220/105, pulse 76 per minute, and she was having Cheyne-Stokes respirations at 24/minute. Temperature was 37.4° C. The general physical examination was non-contributory. On neurological examination her optic discs were flat, no spontaneous venous pulsations were visible, nor were there retinal or sub-hyaloid hemorrhages. The right pupil was 3.5 mm and the left 3.0 mm. Both reacted briskly to light. The eyes were in a constant roving state, but there was a gaze palsy to the left. The corneal reflexes were present but depressed. A left peripheral 7th nerve palsy was present. Tone was increased in the lower extremities. Reflexes were hyperactive throughout with ankle clonus and bilateral Babinski signs. The cerebellar system could not be tested. It was felt that the patient had suffered a pontine hemorrhage. She expired five days after admission.

Routine blood chemistries, hematologic profile, as well as skull and chest roentgenograms and brain scan were normal. A lumbar puncture was not performed.

Necropsy revealed coronary atherosclerosis and bilateral bronchopneumonia. The brain was edematous with obvious enlargement of the left cerebellar hemisphere. There was bilateral uncus herniation as well as herniation of the left cerebellar tonsil into the foramen magnum with compression of the pons and

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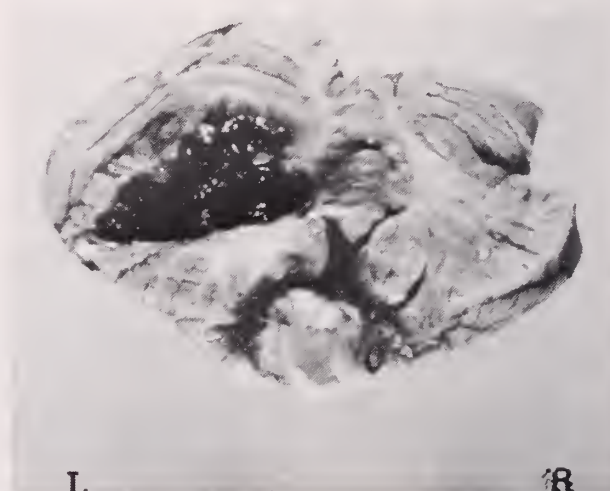


Fig. 1. Cerebellar hemorrhage into left hemisphere.

medulla on the left. Sections through the cerebellum (Fig. 1) revealed a massive but localized area of hemorrhage measuring 3 cm in diameter in the center of the left cerebellar hemisphere.

DISCUSSION

Fifty to 70 percent of cerebellar hemorrhages are secondary to hypertension, and they most often occur from the 6th to 8th decades of life.^{4,6,7} Those that occur in the younger population are often secondary to arteriovenous malformations or blood dyscrasias.⁸

Headache which is often excruciating and suboccipital in location, dizziness, repeated bouts of nausea and vomiting, and the inability to stand or walk are the prominent symptoms.^{5,6} Loss of consciousness is unusual at the onset, but as the hemorrhage progresses coma is common.^{6,7}

The most frequently observed signs are ipsilateral gaze palsy, appendicular (limb) ataxia, peripheral 7th nerve palsy, constricted and reactive pupils, and periodic respirations.^{6,7} The pupils are small but reactive, and frequently the pupil ipsilateral to the hemorrhage is smaller.⁶ Paresis of conjugate lateral gaze to the side of the lesion is a common finding, as is horizontal nystagmus to the ipsilateral side.⁶ Hemiplegia may or may not be present, and it is of questionable value, especially in the light of co-existent ataxia. The presence of a Babinski sign bodes poorly for the survival of the patient.⁶ Patients who present in coma usually have an advanced state of brain dysfunction.^{6,7} The most common signs in this situation are external ophthalmoplegia, respiratory irregularity, and apnea. A minority of comatose patients will have lateralizing cranial nerve signs, most commonly ipsilateral 7th nerve palsy.⁷

Lumbar puncture is a guide to the type of lesion that is present but it is a dangerous procedure because of the increased intracranial pressure and the possibility of a posterior fossa mass lesion.⁵ If performed, a small bore needle should be used and only the amount of fluid needed for the diagnosis should be removed.⁸ The cerebrospinal fluid is bloody in the majority of cases.⁵⁻⁹ In the past, vertebral angiography was the preferred diagnostic procedure,^{5,7} but with the advent of computerized axial tomography this modern procedure is preferred for not only is it quite accurate and rapid, but it is totally non-invasive.⁷

Approximately two-thirds of patients with cerebellar hemorrhage may have altered levels of consciousness but still be responsive on admission.⁶ In the presence of bloody CSF, cerebellar hemorrhage has to be differentiated from hemorrhage of the putamen (60%), thalamus (10%), or pons (10%).⁶ Hemiplegia, hemianesthesia, hemianopsia, facial weakness, and deviation of the eyes to the side of the hemorrhage point to the putamen as the site of the hemorrhage.⁶ Thalamic hemorrhage produces hemisensory loss, hemiplegia, and downward deviation of the eyes as if they were peering at the nose.⁶ The pupils are small and do not react to bright light. In pontine hemorrhage, the patient becomes rapidly comatose, develops flaccid quadriplegia and hyperthermia.⁶ The pupils are pinpoint, reactive, and ocular bobbing may be present.⁶ Syncope, 3rd nerve palsy, hemiplegia, and subhyaloid hemorrhages are commonly seen with rupture of an intracranial aneurysm.

Cerebellar hemorrhage carries a grave prognosis with some 75% of medically treated cases expiring within the first few days, whereas those treated surgically have a much better survival.^{6,7} Stupor and coma are essentially irreversible stages of cerebellar hemorrhage; 19 of 20 such patients in one series died.⁷ Immediate surgery is imperative if the diagnosis is made.^{5,6} Suboccipital craniotomy with evacuation of the clot is the surgical procedure of choice.^{6,8,9}

Most hypertensive cerebellar hemorrhages arise in or near the dentate nucleus, with the superior cerebellar artery being the "artery of cerebellar hemorrhage".¹ In hemorrhages secondary to arteriovenous malformations the clot is usually deeper in the hemisphere, but in either circumstance the hematoma is usually large enough to cause death from medullary compression.

SUMMARY

The case report of a patient who expired from a hypertensive cerebellar hemorrhage has been reported. Unfortunately as in a majority of previously reported cases the diagnosis here was not made until necropsy, although this patient presented with many of the signs of a cerebellar hemorrhage. The etiological and clinical features of cerebellar hemorrhage have been discussed, and certain signs and symptoms are presented, which, if present, should alert the examining physician to the possible presence of cerebellar hemorrhage. Overall the most important factor influencing the outcome is the rapid and correct diagnosis.

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Reminder to M.M.A. Members

CONTINUING MEDICAL EDUCATION ACTIVITY REPORT

The bylaws of the Maine Medical Association were amended in June of 1973 as follows: Chapter I, Section 11, — "Each member of the Maine Medical Association shall be required to report his activities in continuing medical education every year according to a format provided by the Committee on Continuing Medical Education."

Only active, dues-paying members are required to report this year.

Please fill in your activity report promptly and return to the M.M.A. office, P.O. Box 250, Brunswick, Maine 04011.

Rural Medicine: Coronary Care

ROWLAND B. FRENCH, M.D.

This study was prompted by the impression, gained from the care of several heart attack patients, that prompt diagnosis, having the patient keep lying down immobilized until transported to a hospital, and transportation by ambulance with no ambulation at all, might be a large factor in preventing small myocardial infarctions from becoming large ones, and thus be one of the most important parts of coronary care. One patient had been at home, moving around with severe chest pain for three days, then with increasing distress elected to go by ambulance to a hospital, and died on the way. Another patient with infarction refused to stay in the hospital after one day, and went home by ambulance for bed rest, but immediately got up and wandered around the town, and eight weeks later appeared with severe pain and died on the way to the hospital. Another patient had chest pain and was hospitalized when the hospital first had connections with the dataphone system. He felt well, and the ECG report came back as normal, and he had a normal transaminase. He decided to go home after one day, but returned the following day with pain and died fifteen days later. This would suggest that perhaps there is something in rest itself, at least in the early days, or perhaps hours, by a patient with myocardial infarction which makes a difference, at least in some patients, whether or not they survive.

Undoubtedly, patients get along occasionally who have never been treated. The patient's ECG shows an old infarction, and the patient is unaware of having had any particular attack. Other patients have been treated by rest at home, where they were seen several days after the attack took place, and seemed to do well.

One also obtained the impression that when stressful situations appeared to be involved in the onset of the attack, that family problems seemed to predominate.

A review of 26 hospitalized patients with acute myocardial infarctions treated between 1969 and 1974 revealed a patient's age range of 42 to 86 years of age. Most patients had had anterior chest discomfort for several hours prior to coming to the hospital; three only for one-half hour, which was the shortest period of time; one for ten hours; two for two days; one for probably three days; some with increasing chest pain for over a month with then more increased pains usually for several hours. Fourteen patients had previous anginal pain, some for a few months to others for several years. Four patients had had a previous heart attack several years before. Twelve were brought in by ambulance and of these, three patients died. Of the ambulatory group, two died, but it is possible that the sicker patients came by ambulance, so that no conclusion would

seem to be possible. Three patients had diabetes, one was on DBI[®]; several were overweight but only one obese. The cholesterol was elevated moderately on only one, but unknown in several. A review of the histories of the patients revealed possible tensions in only one or two patients. In the rest, tensions were either unknown or nonexistent, and the attacks seemed more related to getting overtired.

The white blood count was elevated in fourteen patients, usually to about 9,000, but in some to as high as 23,500. The SGOT was elevated in most patients but was normal on the day of admission in twelve. In one, it was not done, and in another, the onset of the attack was probably several days prior to entry so that no rise was found. In most patients, the transaminase rose by the second day, in some as high as 450, but more recently in two other cases did not rise until the fifth hospital day with no further recurrence of pain. The ECG was read as normal on the day of admission, or had only nonspecific changes with no suspicion of infarction, in four cases. In two patients, it was thought that they had only repeated anginal attacks, and appeared in no discomfort when the ECG revealed a recent myocardial infarction of a day or two duration. One case had paroxysmal atrial tachycardia occurring two weeks after the onset of an attack. However, in general, despite the use of a monitor in most of the more recent cases, no important arrhythmia was noted or else was missed.

Five of the patients died, one with a seven-year history of angina, having had severe pain for one week, and had lifted heavy potatoes three hours prior to entry. He had been hypotensive one day after entry, responding to metaraminol bitartrate, and had been up in a chair one week after entry. Sixteen days after entry, he went into shock going from commode to bed and expired suddenly, perhaps due to a pulmonary embolism or recurrent infarction. Another patient was an 84-year-old man with hypertension, aortic stenosis and previous infarction, complaining of stomach distress for ten days, then substernal distress. He went into shock soon after entry, and responded not at all to metaraminol bitartrate or attempts at resuscitation. Another case, a 58-year-old woman with history of prolonged diarrhea for several weeks, was in shock, and had pulmonary edema, and had no response to metaraminol bitartrate, diuretics and efforts at resuscitation, and died shortly after entry. Another patient, age 65, with history of angina, went into shock suddenly after possibly overexertion and expired five days after entry. Another case was a 76-year-old man who had chest pain for ten hours at home, had a few ventricular extra systolic beats,

which subsided. His SGOT was 440, his WBC was 21,000. He went into shock after eight hours, at first responding to metaraminol bitartrate, and then developed further shock and died fifteen hours after entry.

Of the patients who did not survive, one was ambulatory for ten hours at home after the attack began, another was active for several days and had lifted heavy potatoes, after the onset of much sub-sternal discomfort. Two other patients had been sick for days at home. In both, it was difficult to say when the attack had started, and both were ambulatory on admission, and this exertion may have been detrimental. The fifth patient may have over-exerted after several days in the hospital, and did not receive heparin for the first two hospital days. In these patients, it would seem that delay and overexertion did play a role.

Eighteen of the patients were placed on heparin for several days. An earlier impression had been that the more severe cases, at least, seemed to be more likely to survive if treated early with heparin. The cases that had had the attack several days before entry were not treated with heparin, as were not two cases during whose stay the ECG findings were quite indefinite, and it was only on repeated tracings that it became clear that they were having a recent attack.

Two cases had cardiac failure develop, and it was suspicious in these, and in the case that may have had a pulmonary embolism or a severe recurrent infarction that they may have been mobilized too rapidly, although there was no good evidence of an aneurysm of the ventricular wall. One wonders if cases should not be individualized rather than all mobilized and discharged by a certain day, and, in the rush to be the first to mobilize, some harm may be done.

Most of these cases stayed in the hospital for about three weeks although getting up on a commode at the bedside as needed. Several cases went home at an earlier interval by ambulance to continue

their bed rest at home, if the home situation made this possible. Others went home by ambulance at the end of three weeks to gradually get ambulatory at home.

In these cases, the cardiac monitor became valuable mostly only after hospital personnel became somewhat familiar with it. The dataphone has been useful, but largely where it was possible to communicate problems with the very cooperative cardiologists that have been available. The drawbacks that existed at first consisted in the placing of too much reliance on normal or only slightly abnormal non-specific changes in the ECG, which was corrected by repeating the ECG and observing the patient for a three-day period, if clinically there was some suspicion of infarction. The other drawback was the time interval for a report, and this was obviated by taking a paper tracing and acquainting oneself of basic ECG reading, if one did not want to send for a stat report on each occasion. This was found to be true particularly in two cases that were thought to have only angina, and the dataphone report the following day showed infarction. It would seem also that patients with myocardial infarction should be largely treated in facilities that have good monitoring capabilities and good abilities in cardiopulmonary resuscitation.

SUMMARY

In summary, the course of several patients with myocardial infarction was reviewed. An attempt was made to compare outcome to early care, but in this limited series, it was not possible to draw a definite conclusion. It was necessary to watch patients with clinically suggestive symptoms for three days before drawing final conclusions from ECG and transaminase determinations. It was suggested that early diagnosis and complete early immobilization may be important factors in the eventual outcome.

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The Financial Physical

ROBERT M. FILES*

I suppose the first place to start on a subject like this is to explain the title. What is a financial physical? What are we talking about?

Since a physical is an examination and finance is the management of monetary affairs, we're talking about an examination of financial management. And what does that encompass?

Before we answer this question, we should take a look at what we have that requires financial management.

First of all, we have a medical practice. Let's call it a business — and like all businesses we have it for the purpose of making a profit (the most profit). This is the common denominator, the objective.

At this point, we could talk for a long time on valuing a business, massage a lot of numbers, and come up with several answers. But in simple terms, if a business produced for its owner an excess of revenue over expenses of \$50,000 a year before proprietary withdrawals and disbursements for personal retirement plans, and we capitalized that amount at 10%, we would have a business worth \$500,000. If we used 5%, we would have a \$1,000,000 business.

For our purpose, it doesn't make any difference whether it's \$500,000, \$1,000,000 or \$2,000,000. The point I want to make is that it's *BIG*. A lot bigger than many of us realize. You may not feel the same way, but when I look at something in terms of total dollar value, it is more in perspective.

Now that we realize we have something more at stake, what should we do about it? What should we do about financial management? What do other businesses do about financial management? For one thing, they usually have a financial officer. Now, I'm not suggesting that you run right out and hire a full time financial officer, although that isn't as ridiculous as it sounds in some instances.

However, you might say, "That's all well and good for ATT, IBM, and others, but I'm just a one-man shop. The basic principles of good, sound business are the same regardless of the size of the operation."

In the organizational structure of any business, there is a financial function which must be monitored. This may be done by the sole proprietor (the chief executive if he has a financial background) *as one of his many responsibilities*, or by whomever he may delegate, such as a financial person, *as his only responsibility*. In either case, the need for financial management is there.

Let's take a look at this financial guy, the "chief financial officer." What's his background? What does he do? His education and experience involve years of accounting and finance. In many instances he was formerly in public practice as a CPA. He has the responsibility for managing the numbers: past, present and future. Some would say (and I agree in certain circumstances) that financial planning and the future are the most important. This becomes academic, however, if one doesn't pass or survive the physical today . . . so let's start with the present.

The chief financial officer has the responsibility for seeing that each of the following functions is operating properly.

General accounting	Internal control
Systems and procedure	Projections
Financial reporting	Cost accounting
Taxes and tax planning	Accounts receivable and payable
Cashier	Other capital expenditures
Investments	Inventory
Real estate	Pensions
Financing	Insurance
Payroll	Training
Cash flow	Budgets

And last but not least, financial planning (the future) *as it applies to each of the above*.

That's a pretty big job, and you may not believe it, but every one of these functions applies to a medical practice. In addition to the foregoing, a doctor has the responsibility for determining whether to conduct his practice as an individual, a partnership, or as a professional association, and also for estate planning.

I could go on and on as to the specifics in each area, but let's just take a few minutes to talk briefly about some of them.

First, what do we mean by "operating properly"? That's an all-inclusive term if there ever was one, but to mention a few things, it means that:

1. Procedures are established and followed.
2. Adequate records are maintained and supported by underlying detail.
3. Reports are timely and meaningful.
4. Collections are current.
5. Internal control is satisfactory and nothing is "falling through the cracks."

In short, it means that everything is up to snuff in all respects; and if it isn't, then taking the necessary steps (the time) to get it there. (This is the key to the whole thing.)

Financial reporting — I realize you don't have a lot of shareholders and you're not listed on the "Big Board." What I'm really talking about is in-

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ternal financial reports, generally referred to as management reports.

Periodic and meaningful financial statements are the most important tools of financial management. They consist primarily of (1) the statement of income, and (2) the balance sheet. These two statements will provide the financial answer to two questions frequently asked a doctor by his patient: (a) How am I doing? (b) What do I have?

The income statement is the financial measure of "how one is doing", i.e., the results of operations for a period of time. Generally I have found, over the years, that an income statement is only available as part of last year's tax return and therefore does not exist for the current year. You wouldn't wait six months to a year to find out how a patient is doing, so why wait that long to find out how you are doing?

Income statements should be prepared and thoroughly reviewed, at least quarterly, if not monthly. It doesn't have to be a big production. It does involve, at the outset, some training and an accounting system that will readily produce financial data in a manner to facilitate preparation of the statements. Again, we get back to systems and procedures.

The balance sheet is the financial measure of "what one has," the financial diagnosis of one's net worth at a given point in time. They are even more non-existent than income statements since they are not required on an individual's tax return. The need for a balance sheet is not as frequent as it is for an income statement: annually or quarterly will generally suffice. Nevertheless, it is just as important as an income statement in other respects; even more so if one is borrowing money.

Record keeping is also a big factor with regards to the balance sheet and each item therein should be *properly* supported by underlying detail. I emphasize the word *properly* because there is a difference between what IRS and the taxpayer feel is *proper*. Once the records are established and maintained, it is a simple matter to prepare a balance sheet.

Poor records are not a crime, although they may result indirectly in a penalty. The main thing is to correct the situation as soon as possible — not when you decide to sell property or the IRS agent walks in. The longer you wait, the more difficult the job becomes.

Taxes — The tax approaches available to a medical practice are so voluminous that it is not my intention to discuss them at this time. Needless to say, taxes are the most important subject within the realm of financial management and therefore warrant a great deal of consideration. Consideration in the form of tax planning, i.e., an in-depth study of the tax aspects of a given course of action *before* such action is taken.

Internal control — The modus operandi of a doctor's office, or any office of similar size, does not lend itself to good internal control, especially in view of the large amount of currency involved. Accordingly, it is all the more important that proper internal controls be maintained where possible.

Cost accounting — One might say, "What's cost accounting got to do with it? I'm not a manufacturing company." The point is that if you can substantiate your fees by cost accounting studies, you will stand a better chance of having them accepted when looking to a third party for payment (no guarantee, though). This automatically leads to the subject of systems and procedure in order to produce the necessary data.

By now you should have a better idea of the true scope of financial management and realize this function must be performed in its entirety according to generally accepted principles of financial management if one is to "run a tight ship" and achieve his desired objective.

The following questionnaire may be used as a guide to help you evaluate your financial operations.

- | | Yes | No | Don't Know |
|--|-----|----|------------|
| 1. Are your general accounting records maintained in a satisfactory manner? | | | |
| 2. Are fees established on the basis of periodic cost studies? | | | |
| 3. Are bank accounts reconciled monthly? | | | |
| 4. Are accounts receivable balanced with the control account monthly? | | | |
| 5. Are accounts receivable aged monthly? | | | |
| 6. Are all services rendered billed and/or collected? | | | |
| 7. Are you receiving the appropriate discounts? | | | |
| 8. Are real estate, investments and other asset accounts supported by appropriate detail? | | | |
| 9. Are supplies under control? | | | |
| 10. Does your organizational structure (proprietorship, partnership or professional association) provide the desired benefits? | | | |
| 11. Are your tax plans set forth and periodically reviewed in the light of current income? | | | |
| 12. Are payroll deposits made in | | | |

Continued on Page 236

Syphilis — CDC Recommended Treatment Schedules, 1976

The following recommendations were established by the Venereal Disease Control Advisory Committee after deliberation with therapy experts.***

Few data have been published on the treatment of syphilis since CDC revised these recommendations in 1968. Penicillin continues to be the drug of choice for all stages of syphilis. Every effort should be made to document penicillin allergy before choosing other antibiotics because these antibiotics have been studied less extensively than penicillin. Physicians are cautioned to use no less than the recommended dosages of antibiotics.

EARLY SYPHILIS (primary, secondary, latent syphilis of less than 1 year's duration)

- (1) Benzathine penicillin G — 2.4 million units total by intramuscular injection at a single session. *Benzathine penicillin G is the drug of choice because it provides effective treatment in a single visit.*[†] **OR**
- (2) Aqueous procaine penicillin G — 4.8 million units total: 600,000 units by intramuscular injection daily for 8 days. **OR**
- (3) Procaine penicillin G in oil with 2% aluminum monostearate (PAM) — 4.8 million units total by intramuscular injection: 2.4 million units at first visit, and 1.2 million units at each of 2 subsequent visits 3 days apart. *Although PAM is used in other countries, it is no longer available in the United States.*

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Patients who are allergic to penicillin:

- (1) Tetracycline hydrochloride^{††} — 500 mg 4 times a day by mouth for 15 days. **OR**
- (2) Erythromycin (stearate, ethylsuccinate or base) — 500 mg 4 times a day by mouth for 15 days.

These antibiotics appear to be effective but have been evaluated less extensively than penicillin.

SYPHILIS OF MORE THAN 1 YEAR'S DURATION (latent syphilis of indeterminate or more than 1 year's duration, cardiovascular, late benign, neurosyphilis)

- (1) Benzathine penicillin G — 7.2 million units total: 2.4 million units by intramuscular injection weekly for 3 successive weeks. **OR**
- (2) Aqueous procaine penicillin G — 9.0 million units total: 600,000 units by intramuscular injection daily for 15 days.

The optimal treatment schedules for syphilis of greater than 1 year's duration have been less well established than schedules for early syphilis. In general, syphilis of longer duration requires higher-dose therapy. Although therapy is recommended for established cardiovascular syphilis, there is little evidence that antibiotics reverse the pathology associated with this disease.

Cerebrospinal fluid (CSF) examination is mandatory in patients with suspected, symptomatic neurosyphilis. This examination is also desirable in other patients with syphilis of greater than 1 year's duration to exclude asymptomatic neurosyphilis.

Published studies show that a total dose of 6.0-9.0 million units of penicillin G results in a satisfactory clinical response in approximately 90% of patients with neurosyphilis. There is more published clinical experience with short-acting penicillin preparations than with benzathine penicillin G. Some clinicians prefer to hospitalize patients with neurosyphilis, particularly if the patient is symptomatic or has not responded to initial therapy. In these instances they treat patients with 12-24 million units of aqueous crystalline penicillin G given intravenously each day (2-4 million units every 4 hours) for 10 days.

[†] Italics indicate commentary.

^{††} Food and some dairy products interfere with absorption. Oral forms of tetracycline should be given 1 hour before or 2 hours after meals.

Patients who are allergic to penicillin:

- (1) Tetracycline hydrochloride — 500 mg 4 times a day by mouth for 30 days. **OR**
- (2) Erythromycin (stearate, ethylsuccinate or base) — 500 mg 4 times a day by mouth for 30 days.

There are NO published clinical data which adequately document the efficacy of drugs other than penicillin for syphilis of more than 1 year's duration. Cerebrospinal fluid examinations are highly recommended before therapy with these regimens.

SYPHILIS IN PREGNANCY

Evaluation of Pregnant Women

All pregnant women should have a nontreponemal serologic test for syphilis, such as the VDRL or RPR test, at the time of the first prenatal visit. The treponemal tests such as the FTA-ABS test should not be used for routine screening. In women suspected of being at high risk for syphilis, a second nontreponemal test should be performed during the third trimester. Seroreactive patients should be expeditiously evaluated. This evaluation should include a history and physical examination, as well as a quantitative nontreponemal test and a confirmatory treponemal test.

If the FTA-ABS test is nonreactive and there is no clinical evidence of syphilis, treatment may be withheld. Both the quantitative nontreponemal test and the confirmatory test should be repeated within 4 weeks. If there is clinical or serologic evidence of syphilis or if the diagnosis of syphilis cannot be excluded with reasonable certainty, the patient should be treated as outlined below.

Patients for whom there is documentation of adequate treatment for syphilis in the past need not be retreated unless there is clinical or serologic evidence of reinfection such as darkfield-positive lesions or a 4-fold titer rise of a quantitative nontreponemal test.

- A. For patients at all stages of pregnancy who are not allergic to penicillin:** Penicillin in dosage schedules appropriate for the stage of syphilis as recommended for the treatment of nonpregnant patients.
- B. For patients of all stages of pregnancy who are allergic to penicillin:** Erythromycin (stearate, ethylsuccinate or base) in dosage schedules appropriate for the stage of syphilis, as recommended for the treatment of nonpregnant patients. Although these erythromycin schedules appear safe for mother and fetus, their efficacy is not well established. Therefore, the documentation of penicillin allergy is particularly important before treating a pregnant woman with erythromycin. *Erythromycin estolate and tetracycline are not recommended for syphilitic infections in pregnant women because of potential adverse effects on mother and fetus.*

Follow-up

Pregnant women who have been treated for syphilis should have monthly quantitative nontreponemal serologic tests for the remainder of the current pregnancy. Women who show a 4-fold rise in titer should be retreated. After delivery, follow-up is as outlined for nonpregnant patients.

CONGENITAL SYPHILIS

Congenital syphilis may occur if the mother has syphilis during pregnancy. If the mother has received adequate penicillin treatment during pregnancy, the risk to the infant is minimal. However, all infants should be examined carefully at birth and at frequent intervals thereafter until nontreponemal serologic tests are negative.

Infected infants are frequently asymptomatic at birth and may be seronegative if the maternal infection occurred late in gestation. Infants should be treated at birth if maternal treatment was inadequate, unknown, with drugs other than penicillin, or if adequate follow-up of the infant cannot be ensured.

Infants with congenital syphilis should have a CSF examination before treatment.

Infants with abnormal CSF:

- (1) Aqueous crystalline penicillin G, 50,000 units/kg intramuscularly or intravenously daily in 2 divided doses for a minimum of 10 days. **OR**
- (2) Aqueous procaine penicillin G, 50,000 units/kg intramuscularly daily for a minimum of 10 days.

Infants with normal CSF:

Benzathine penicillin G, 50,000 units/kg intramuscularly in a single dose. Although benzathine penicillin has been previously recommended and widely used, published clinical data on its efficacy in congenital neurosyphilis are lacking. If neurosyphilis cannot be excluded, the procaine or aqueous penicillin regimens are recommended. Since cerebrospinal fluid concentrations of penicillin achieved after benzathine penicillin are minimal to nonexistent, these revised recommendations seem more conservative and appropriate until clinical data on the efficacy of benzathine penicillin can be accumulated. Other antibiotics are not recommended for neonatal congenital syphilis.

Penicillin therapy for congenital syphilis after the neonatal period should be with the same dosages used for neonatal congenital syphilis. For larger children the total dose of penicillin need not exceed the dosage used in adult syphilis of more than 1 year's duration. After the neonatal period, the dosage of erythromycin and tetracycline for congenital syphilitics who are allergic to penicillin should be individualized but need not exceed dosages used in adult syphilis of more than 1 year's duration. Tetracycline should not be given

to children less than 8 years of age.

FOLLOW-UP AND RETREATMENT

All patients with early syphilis and congenital syphilis should be encouraged to return for repeat quantitative nontreponemal tests 3, 6, and 12 months after treatment. Patients with syphilis of more than 1 year's duration should also have a repeat serologic test 24 months after treatment. Careful follow-up serologic testing is particularly important in patients treated with antibiotics other than penicillin. Examination of CSF should be planned as part of the last follow-up visit after treatment with alternative antibiotics.

All patients with neurosyphilis must be carefully followed with serologic testing for at least 3 years. In addition, follow-up of these patients should include clinical reevaluation at 6-month intervals and repeat CSF examinations, particularly in patients treated with alternative antibiotics.

The possibility of reinfection should always be considered when retreating patients with early syphilis. A CSF examination should be performed before retreatment unless reinfection and a diagnosis of early syphilis can be established.

Retreatment should be considered when:

- (1) Clinical signs or symptoms of syphilis persist or recur;
- (2) There is a sustained 4-fold increase in the titer of a nontreponemal test;
- (3) An initially high-titer nontreponemal test fails to show a 4-fold decrease within a year.

Patients should be retreated with the schedules recommended for syphilis of more than 1 year's duration. In general, only 1 retreatment course is indicated because patients may maintain stable, low titers of nontreponemal tests or have irreversible anatomical damage.

EPIDEMIOLOGIC TREATMENT

Patients who have been exposed to infectious syphilis within the preceding 3 months and other patients who on epidemiologic grounds are at high risk for syphilis should be treated as for early syphilis. Every effort should be made to establish a diagnosis in these cases.

Reported by Venereal Disease Control Div., Bur of State Services, CDC.

THE FINANCIAL PHYSICAL — Continued from Page 233

- accordance with IRS instructions?
13. Are the accounting systems and procedures operating satisfactorily?
 14. Do the accounting systems and procedures provide the necessary financial data?
 15. Is cash flow maximized?
 16. Are the peaks and valleys of cash flow eliminated?
 17. Do you have a qualified pension or H.R. 10 plan?
 18. Are separate pension records maintained?
 19. Are the required pension reports and disclosures being made?
 20. Do you have a budget?
 21. Is your budget being adhered to?
 22. Do you have adequate insurance coverage?
 23. Is your insurance coverage reviewed annually?
 24. Has your internal control been strengthened as much as possible?
 25. Do you receive an income statement monthly?
 26. Do you prepare a balance sheet quarterly, or at least annually?
 27. Are your financial statements on an accrual basis?
 28. Do you prepare projections on financial data?
 29. Are your financial plans established and monitored?
 30. Have you considered EDP accounting with regards to a) general books and records, b) financial reporting, c) billing, d) insurance records, e) payroll?
 31. Do you have an estate plan?

If the answer to any question is "no" or "don't know," are you doing something about it?

Don't forget to take care of yourself . . . financially, that is.

From the Secretary's Notebook

Summary of 1976 Annual Meeting of the

M.M.A. House of Delegates

June 5 and 6, 1976 at Rockport, Maine

The 123rd annual session of the M.M.A. House of Delegates was held at the Treadway-Samoset Resort in Rockport, Maine with a registered attendance of sixty-seven delegates and alternates, and twenty-eight guests. The first session was held on Saturday at 2:00 P.M., and the second session on Sunday at 2:00 P.M. Euclid M. Hanbury, Jr., M.D., President of the M.M.A. called to order the meetings of the House, which were presided over by George W. Bostwick, M.D., Speaker of the House.

Election of Speaker and Vice Speaker of the House of Delegates for 1976-77 — George W. Bostwick, M.D. was re-elected Speaker of the House, and Richard M. Swengel, M.D., Vice Speaker of the House.

Budget for 1977 — The reference committee recommended that the Budget, as presented be approved, with the exception of \$35,000 for the Assistant Executive Director, and this was *so voted*. A further suggestion was made that the Assistant E. D.'s salary be referred back to the Executive Committee. A motion was made that up to \$35,000 be included in the budget for implementation of the hiring of an Assistant to the E. D., along the guidelines as established by the House of Delegates (see resolution), and this was *approved*.

Committee on Nominations — A slate was presented in April at the Interim Meeting of the House of Delegates, and at this meeting for vote, and the following officers elected:

President-elect

Donald L. Anderson, M.D.

Executive Committee

- 1st District — Maurice Ross, M.D.
- 5th District — David L. Phillips, M.D.
- 6th District — Harold E. Knuuti, M.D.

Dr. Richard M. Swengel of Lewiston was elected to complete Dr. Wright's term for the 7th District, and Dr. Eric Nicholas of Mars Hill to complete Dr. Ouellette's term for the 9th District.

The Standing Committees, as recommended by the Committee on Nominations, were *approved*,

with the addition of Drs. Eric Nicholas and John Menges on the Emergency Medical Services Committee.

Reports (not included in the House of Delegates' folder) —

Executive Director — Dr. Hanley spoke to the delegates on the subjects of malpractice, JUA (Joint Underwriting Authority), the Flu Vaccination Program, National Health Insurance, the Health Manpower Bill, and the Proposed Certificate of Need Program.

Committee on Health Care Financing — Dr. Lightbody, Chairman, gave a detailed committee report at the April meeting of the House of Delegates and reported that since that time, the M.M.A. has added a major medical program to its group BCBS plan. He also spoke of consumerism and representation of physicians on the BCBS Board. A request from the Department of Human Services for the committee to establish a Statewide fee schedule for Medicaid has been received, Dr. Lightbody added. An Ad Hoc Committee was appointed to look into such a schedule, and Dr. Dewey Richards reported the recommendations of this group, which were "That a Statewide fee schedule for each of the specialties be established. It is recommended that the prevailing charge as defined by Medicare be used as the basis of the fee schedule. The prevailing charge is calculated by determining the median fee for each physician, combining the fees, and taking the 75th percentile of that array." The reference committee recommended that this report be referred back to the full Committee on Health Care Financing for a report to the House of Delegates at its Fall Meeting, and this was *approved*.

Care of the Disadvantaged — The Chairman, Dr. John Pearson, referred specifically to the name of the Committee which he would like to see changed back to Rural Health Committee. The reference committee recommended acceptance of this report and filing for information, and this was *approved*.

Committee on Medical Care in Maine's Prisons — Dr. Donald Weaver, Chairman, reported on the first meeting of this committee which dealt with the question of excess drug use in prisons, the dis-

pensing, and the problem of drug administration by certain personnel in penal institutions. A resolution on these matters was presented by the committee and appears under "resolutions."

Printed reports not requiring action (resolutions from committees appear elsewhere in this summary), and *accepted* for information were as follows: Committees — Emergency Medical Services, Liaison with the Maine Hospital Association, Amy W. Pinkham Fund, Burn Advisory, Liaison with the Maine Bar Association, Peer Review (with a reservation as to the activities of the Pine Tree Organization), Diabetes, Vision, Continuing Education, Maternal and Child Welfare; Reports of Secretary-Treasurer, President of the Auxiliary, Executive Committee members and Delegates to Out-of-State Medical Society meetings.

RESOLUTIONS

Membership — The original resolution was presented by the Executive Committee, and the following substitute resolution recommended by the Reference Committee and *approved*:

WHEREAS, the Executive Committee feels strongly that there should be unified membership within the Association, and

WHEREAS, it is now possible for a person to be a member of a county medical society without belonging to the Maine Medical Association,

NOW THEREFORE BE IT RESOLVED THAT Section 1 of Chapter 1 of the Bylaws shall be and is hereby amended, by the addition of a second and third sentence to follow the first one, and to read as follows: "All component Society members shall, on election to such membership or upon adoption of this Section, become members of this Association. Discontinuation of Association membership shall terminate concomitantly such component society membership."

Delinquent Dues — Presented by the Executive Committee, this was *approved*:

WHEREAS, the Executive Committee feels strongly that persons dropped from membership for nonpayment of dues or assessments should not be allowed to rejoin at a later date entirely free of responsibility for these dues or assessments,

NOW THEREFORE BE IT RESOLVED THAT Section 1 of Chapter VIII of the Bylaws shall be and is hereby amended by the addition of a sentence following the present last sentence, to read "Any member suspended for nonpayment of dues must satisfy all debts to the Association, including unpaid dues, before reinstatement or re-election to membership."

(Speaker's comments — If someone is suspended for nonpayment of 1971 dues and rejoins

in 1975, he has to pay the 1971 dues (not 1972, 1973 or 1974).

Name Change — Presented by the Section on Otolaryngology, the following resolution was *approved*:

WHEREAS, the discipline of maxillo-facial surgery is not the exclusive domain of any one specialty, and is included in the field of otolaryngology, and

WHEREAS, historically, otolaryngologists have been intimately and extensively involved in the provision of this form of medical care, and

WHEREAS, a number of medical school departments are known as the Department of Otolaryngology and Maxillo-facial Surgery; there be it

RESOLVED, That the Medical Society of the State of Maine rename the Section on Otolaryngology to the Section on Otolaryngology and Maxillo-facial Surgery.

Assistant Executive Director — Presented by the Reference Committee, this resolution was *approved*:

WHEREAS, the original intent of the House of Delegates in creating the position of the Assistant Executive Director was to increase the efficiency of the Maine Medical Association in dealing with government agencies and to facilitate the management of the Executive Director's office, and

WHEREAS, the consensus was that the position would best be served by a professional administrator, with a strong legal and business background, and

WHEREAS, the possibilities of conflict of interest and inappropriateness in the method of hiring has been questioned,

NOW THEREFORE BE IT RESOLVED, that the House of Delegates direct the Executive Committee to reinstate the search for an Assistant Executive Director, who will fulfill the specifications as set forth in an appropriate job description, and that the strongest consideration be given to a non-physician administrator.

A later motion was made for re-consideration of the above resolution and it was *defeated*.

Direct Billing — This resolution, presented by the Aroostook County Medical Society, asking that "the Executive Committee of the Maine Medical Association explore a legislative action providing the Maine physician to have the option of billing patients directly or accepting assignment under the Medicaid program" was *defeated*.

Contract or Agreement — The original resolution, submitted by the Penobscot County Medical Society, was not acted upon, and a substitute resolution presented by the Reference Committee, and

approved as follows:

BE IT RESOLVED, that the Maine Medical Association continue, through its Health Care Finance Committee, to work with third-party payers, but that they avoid any implication that they are negotiating any contract or agreement for a Maine Medical Association member.

High Risk Newborns — This resolution, submitted by the Committee on Maternal and Child Welfare, was *approved* as presented:

WHEREAS, the House of Delegates of the Maine Medical Association at its annual meeting on June 11, 1972, recommended a survey of the then existing facilities for the intensive care of high risk newborns in this State,

WHEREAS, such a survey was conducted and published in March, 1973, under the auspices of the State Comprehensive Health Planning Agency,

WHEREAS, this survey recommended that a neonatal intensive care unit be established at the Maine Medical Center in Portland,

WHEREAS, the geographic distribution of the State requires that some very sick infants be transported almost as much as 400 miles to this neonatal intensive care unit at the Maine Medical Center in Portland,

WHEREAS, the appropriate facilities and personnel are crucial for the survival of these sick infants in transport,

THEREFORE, BE IT RESOLVED that the House of Delegates of the Maine Medical Association, recognizing that there is existing State support for neonatal educational services, recommends that there be a system supported by either increased public or private funds to provide a program for appropriate training of personnel involved and for the actual transportation of high risk newborns requiring the care of the neonatal intensive care unit at the Maine Medical Center, and,

THEREFORE, BE IT FURTHER RESOLVED that the program arrange for the distribution throughout the State of personnel well-trained in the transport of sick newborns, and,

THEREFORE, BE IT FURTHER RESOLVED that copies of this resolution be sent to the Governor of the State, the Commissioner of Human Services, and to all appropriate agencies involved in health care, planning, and emergency medical care throughout the State.

Malpractice #1 — A resolution, listing 14 points, was presented by Dr. Thomas Shields of the Androscoggin County Medical Society. The resolution was amended and sent to the Executive Committee as a working document.

Malpractice #2 — Also presented by the Androscoggin County Medical Society, this resolution

instructed the M.M.A. to "conduct immediate a *voluntary* assessment of \$100.00 from each member of the Association to create a special fund to be used for 1) creating public and legislative awareness of the problems of malpractice and malpractice insurance, 2) protecting the public interest in solving these problems, and 3) investigation for clearer factual information in these areas. This fund shall be administered by an ad hoc committee of the Maine Medical Association, one or two members representing each county, the members appointed by their county medical society, and a chairman appointed by the Executive Committee of the M.M.A., with power to use funds as the ad hoc committee sees fit, and with accountability to the Executive Committee of the M.M.A. for fund expenditure, and application of any remaining funds to a M.M.A. building fund."

Upon recommendation of the Reference Committee, this resolution was *defeated*.

CME Requirement — This resolution was presented by the Cumberland County Medical Society originally, but the Reference Committee entered a substitute resolution, which was *approved* as follows:

WHEREAS, the concepts of continuing medical education have always been endorsed by the Maine Medical Association as a method by which its members could remain current in their medical expertise and

WHEREAS, 14 state medical associations currently have made a policy decision to require continuing medical education as a condition of membership and

WHEREAS, 6 medical specialty societies have made a policy decision to require CME as a condition of membership and

WHEREAS, all 22 medical specialty boards have established a policy to provide recertification, 10 of these having established dates on which recertification will begin and

WHEREAS, medical practice acts in 10 states give the state board of medical examiners authority to require evidence of continuing medical education as a condition for reregistration of the license to practice medicine and

WHEREAS, the Physicians Recognition Award provides a means for documenting CME for all physicians in any field of medicine and an increasing number of Maine physicians have achieved the PRA award in the past 3 years, and,

BE IT RESOLVED, that the Maine Medical Association adopt a policy requiring a minimum of 150 hours of Continuing Medical Education in a period of three (3) years, in order to maintain membership in the Maine Medical Association;

BE IT FURTHER RESOLVED, that this policy take force on January 1, 1977, so that all members must be certified by January 1, 1980.

Members will be eligible for certification beginning on January 1, 1977;

AND BE IT FURTHER RESOLVED, that certification be by one of the following mechanisms.

1. Holding a current Physicians Recognition Award.
2. Active membership in the AAFP or other organization acceptable to the Committee on Continuing Medical Education, or
3. Documentation of 150 hours of Continuing Medical Education as defined by the following criteria:

Category 1 — CME Activities with Accredited Sponsorship (60 hours required)	No limit
Category 2 — CME Activities with Non-accredited Sponsorship	45 hours
Category 3 — Medical Teaching	45 hours
Category 4 — Papers, Publications, Books and Exhibits	40 hours
Category 5 — Non-supervised individual CME Activities	45 hours
Category 6 — Other Meritorious Learning Experiences	45 hours

AND BE IT FURTHER RESOLVED, that the Committee on Continuing Medical Education be directed to formulate rules and regulations governing the administration of this policy by the December meeting.

Medical Care in Prisons — The original resolution was presented by the Committee on Medical Care in Prisons, but the Reference Committee submitted a substitute resolution and it was *approved* as follows:

WHEREAS it is reasonable to have a stated policy governing the administration of medication in Maine Penal Institutions,

NOW THEREFORE BE IT RESOLVED that the Maine Medical Association endorse the following principles:

1. That the Maine Medical Association endorse the prescription medications that are to be used only on the treatment of specific medical and psychiatric disorders, and under the direction of a physician.
2. Medications should not be used to solve administrative or social problems.
3. In view of the increased risk of drug abuse in a penal population, analgesic and psychotropic agents should be prescribed in such a manner that the smallest effective dose of the most innocuous agent with the best abuse potential be used, and automatic stop orders be mandatory.

4. Prison medication use should be analyzed often and reviewed by the appropriate administrative channels.

Reports of Reference Committees — Recommendations (not listed elsewhere in this summary), as *approved* by the House of Delegates, are as follows:

Mental Health Study Commission — This report recommended that the commission be dissolved because of "the continuing inability of the committee to meet with even forty percent attendance and the probability that our committee goals are being and/or will be pre-empted by governmental entities." The report was *accepted* and the Reference Committee suggested that the Executive Committee study the feasibility of continuing this with a Standing Committee on Mental Illness. This was *approved*.

AMA-ERF Committee — The Reference Committee recommended acceptance of the report, and suggested that the Executive Committee consider whether or not this committee is necessary in the future, and this was *approved*.

A. H. Robins Community Service Award — This award for 1976 was presented to Dr. William L. MacVane of Portland.

Maine Blue Cross and Blue Shield Award of Appreciation — This year, three awards were given. Recipients were Drs. Alan Elkins and Robert McAfee of Portland and Dr. Richard Swengel of Lewiston.

Out-of-State Delegates — The following delegates spoke briefly of the major problems in their respective states and extended greetings: Dr. Bernard O. Nemoitin, Connecticut; Dr. Russell Hager, Rhode Island; Dr. Harry M. Rowe, Vermont; Dr. Russell J. Rowell, Massachusetts; and Dr. Ralph S. Emerson, New York.

Blue Shield Survey — Mr. Thomas Cathcart of Maine BCBS reported that BS has been visiting county societies and distributing questionnaires in an effort to gather the opinions of Maine physicians on the complaints and weaknesses of the Blue Shield program. They now have to work with 9 different committees representing various interests around the State. It will be a couple of months before any decisions are made on changes in the Blue Shield product, Mr. Cathcart said. Items discussed were usual and customary coverage, and office laboratory coverage.

Medical School for Maine — Dr. Donald Robertson of Milbridge spoke on the current status and

Continued on Page 245

Famous Fighters



JOHN L. SULLIVAN
Bare-knuckles heavyweight champion
1882-1892

NEOSPORIN® Ointment (polymyxin B-bacitracin-neomycin) is a famous fighter, too.

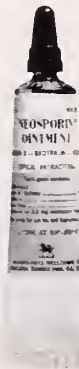
Provides overlapping, broad-spectrum antibacterial action to help combat infection caused by common susceptible pathogens (including staph and strep).

Each gram contains: Aerosporin® brand Polymyxin B Sulfate 5,000 units; zinc bacitracin 400 units; neomycin sulfate 5 mg (equivalent to 3.5 mg neomycin base); special white petrolatum qs in tubes of 1 oz and 1/2 oz and 1/32 oz (approx.) foil packets.

INDICATIONS: Therapeutically (as an adjunct to systemic therapy when indicated) for topical infections, primary or secondary, due to susceptible organisms, as in: • infected burns, skin grafts, surgical incisions, otitis externa • primary pyodermas (impetigo, ecthyma, sycosis vulgaris, paronychia) • secondarily infected dermatoses (eczema, herpes, and seborrheic dermatitis) • traumatic lesions, inflamed or suppurating as a result of bacterial infection.

Prophylactically, the ointment may be used to prevent bacterial contamination in burns, skin grafts, incisions, and other clean lesions. For abrasions, minor cuts and wounds accidentally incurred, its use may prevent the development of infection and permit wound healing. **CONTRAINDICATIONS:** Not for use in the eyes or external ear canal if the eardrum is perforated. This product is contraindicated in those individuals who have shown hypersensitivity to any of the components.

WARNING: Because of the potential hazard of nephrotoxicity and ototoxicity due to



neomycin, care should be exercised when using this product in treating extensive burns, trophic ulceration and other extensive conditions where absorption of neomycin is possible. In burns where more than 20 percent of the body surface is affected, especially if the patient has impaired renal function or is receiving other aminoglycoside antibiotics concurrently, not more than one application a day is recommended. **PRECAUTIONS:** As with other antibacterial preparations, prolonged use may result in overgrowth of nonsusceptible organisms, including fungi. Appropriate measures should be taken if this occurs. **ADVERSE REACTIONS:** Neomycin is a not uncommon cutaneous sensitizer. Articles in the current literature indicate an increase in the prevalence of persons allergic to neomycin. Ototoxicity and nephrotoxicity have been reported (see Warning section).

Complete literature available on request from Professional Services Dept. PML.



Burroughs Wellcome Co.
Research Triangle Park
North Carolina 27709

President
Maine Medical Association
1976-1977



RICHARD C. LECK, M.D.

Richard C. Leck, M.D. of Bath, Maine became the 127th President of the Maine Medical Association at the 123rd annual session banquet on June 7, 1976. He has represented his District on the Executive Committee of the Maine Medical Association since 1972.

Dr. Richard C. Leck was born on February 12, 1931 in Newark, N.J. to Walter and Helen Kasschau Leck.

Dr. Leck's primary and secondary education was obtained in public schools in New Jersey, and he graduated from Bernards High School in Bernardsville, New Jersey in 1949.

Following high school, Dr. Leck attended the College of the University of Chicago, receiving an A.B. in 1952 and an S.B. in 1955. During the years 1953-1955, he worked as a student technician in the Ben May Laboratory for Cancer Research headed by Charles B. Huggins, M.D.

Dr. Leck began his medical school studies at the University of Chicago in 1955 and graduated in 1959. He served a rotating internship at the University of Chicago Hospitals and Clinics from 1959 to 1960, and then completed a residency in Pediatrics at the Bobs Roberts Memorial Hospital of the University of Chicago Hospitals.

Dr. Leck served in the USAF (Medical Corps) at Loring AFB, Limestone, Maine, from 1962-1964.

In 1968, following completion of a residency in Pathology at the University of Colorado Medical Center in Denver, he entered the practice of pathology in the Quad-Cities area in Illinois and Iowa, and then, in 1970, moved to Maine where he has practiced pathology with Nelson Blackburn, M.D. in the Bath area since July of 1970.

Dr. Leck is a member of the Maine Medical Association, and the AMA, is licensed in Maine and California, is certified by the American Board of Pathology in Pathologic Anatomy and Clinical Pathology and is a fellow in the College of American Pathologists and in the American Society of Clinical Pathologists. He is on the staff of Bath Memorial Hospital in Bath, Regional Memorial Hospital and Parkview Memorial Hospital in Brunswick, Miles Memorial Hospital in Damariscotta, St. Andrews Hospital in Boothbay Harbor and on the courtesy staff at the Pen-Bay Medical Center in Rockport.

Dr. Leck resides with his wife Esther and five children on a working farm in Woolwich.

Executive Committee Members Elected at the 123rd Annual Session of the Maine Medical Association

Rockport, Maine

June 5-8, 1976

President

RICHARD C. LECK, M.D.
Bath

President-elect

DONALD L. ANDERSON, M.D.
Lewiston

Sixth District

HAROLD E. KNUUTI, M.D.
Belfast

Executive Committee Chairman

DOUGLAS R. HILL, M.D.
South Portland

Seventh District

RICHARD M. SWENGEL, M.D.
Lewiston

First District

MAURICE ROSS, M.D.
Saco

Ninth District

ERIC F. NICHOLAS, M.D.
Mars Hill

Fifth District

DAVID L. PHILLIPS, M.D.
Rumford

Speaker of the House

GEORGE W. BOSTWICK, M.D.
Newcastle

Dr. Donald L. Anderson was elected President-elect and Dr. George W. Bostwick, Speaker of the House. The following physicians were elected to the Executive Committee: Dr. Douglas R. Hill, *Chairman* (1976-1977); Dr. Maurice Ross, First District (1976-1979); Dr. David L. Phillips, Fifth District (1976-1979); Dr. Harold E. Knuuti, Sixth District (1976-1979); Dr. Richard M. Swengel, Seventh District (1976-1977), to complete Dr. Herbert J. Wright, Jr.'s unexpired term; and Dr. Eric F. Nicholas, Ninth District (1976-1978), to complete Dr. Benoit Ouellette's unexpired term.

DR. ANDERSON was born in Caribou, Maine on April 4, 1915, son of William L. and Geraldine M. S. Anderson. He was graduated from Caribou High School in 1931, the University of Maine in 1935 and received his medical degree from Boston University School of Medicine in 1940. Dr. Anderson interned at the Eastern Maine General Hospital from 1940 to 1941. He served in the military from 1941 to 1945, retiring from the Reserves with the rank of Colonel in 1963. From 1945 to 1948, he served a residency in Urology at the Central Maine General Hospital. A board certified Urologist, Dr. Anderson has practiced in Lewiston since 1948.

He is a member and former Secretary-Treasurer of the Androscoggin County Medical Association, the Maine Medical Association, the American Medical Association and the American Urological Association. Dr. Anderson served on the M.M.A. Executive Committee for the Seventh District (Androscoggin) from 1971 to 1974.

His wife, Dorothy, is also a physician.

DR. HILL of South Portland was born in Portland on April 22, 1927, son of Carlos L. and Vivian L. Hill. He was graduated from South Portland High School in 1945, Bowdoin College in 1950, and received his medical degree from the University of Rochester School of Medicine in 1954. Following an internship and residency at the Rhode Island Hospital in Providence, Dr. Hill began practice in South Portland. He is certified by the American Board of Family Practice. Dr. Hill has served on the Executive Committee since 1974.

He is a member of the Cumberland County Medical Society (and former President), the Maine Medical Association, the American Medical Association, the American Academy of Family Physicians, and is President-elect of the Maine Chapter, American Academy of Family Physicians.

Dr. Hill, his wife and children reside in Cape Elizabeth.



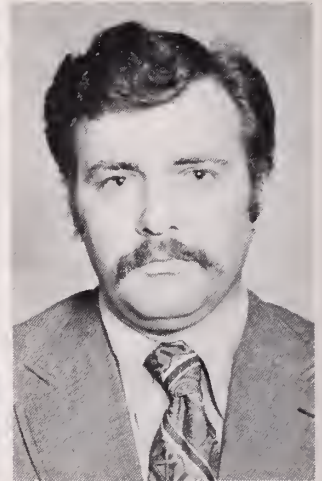
DR. ANDERSON



DR. HILL



DR. ROSS



DR. PHILLIPS

DR. ROSS of Saco was born in Biddeford, Maine on July 5, 1915, son of Abraham E. and Fannie I. Ross. He was graduated from Bowdoin College in 1936 and received his medical degree from Yale University School of Medicine in 1940. Following an internship at the Long Island College Hospital and residency at the University of Chicago Clinics, Dr. Ross served in the U.S. Army as a Major from 1942 to 1946. He located in Saco in 1947, specializing in Pediatrics. Dr. Ross is affiliated with the Webber Hospital in Biddeford and the Maine Medical Center in Portland.

He is a member of the York County Medical Society (and former President), the Maine Medical Association, the American Medical Association and the American Academy of Pediatrics.

Dr. Ross and his wife, Eleanor, reside in Saco.

DR. PHILLIPS of Rumford was born there on January 22, 1938, son of Kenneth M. and Margaret R. Phillips. He was graduated from Bates College and received his medical degree from Tufts University School of Medicine in 1964. Dr. Phillips served a rotating internship from 1964 to 1965, and a residency in General Surgery from 1967 to 1971 at the Maine Medical Center. He served in the U.S. Army Reserve as a Captain from 1964 to 1971. He has practiced in Rumford as a Family Practitioner from 1965 to 1967 and in General and Vascular Surgery from 1971 to the present, and is on the active staff and is Chief of the Department of Surgery at the Rumford Community Hospital and is on the courtesy staff at the Maine Medical Center.

Dr. Phillips is a member of the Oxford County Medical Society (and former Secretary), the Maine Medical Association, the Maine Vascular Society, the American College of Surgeons and is a Diplomate of the American Board of Surgery. He is also a member of the M.M.A. Peer Review Committee and the M.M.A. Nominating Committee, a Delegate to the M.M.A. House of Delegates, and is on the Executive Committee of the Maine Chapter, American College of Surgeons.

DR. KNUUTI of Searsport was born in Quincy, Massachusetts on March 8, 1927, son of Emil Wesner and Bertha Miekka Knuuti. He was graduated from Harvard University and received his medical degree from Tufts University School of Medicine in 1958. Dr. Knuuti interned at the Newton Wellesley Hospital, served a residency in Family Practice in Hanford, California, and attended the U.S. Naval School of Aviation Medicine at Pensacola, Florida. From 1960 to 1962, he served on active duty in the U.S. Navy. Following this, Dr. Knuuti served residencies in Internal Medicine at the Berkshire Medical Center in Pittsfield, Massachusetts and the Albany Medical Center Hospital in New York. He practiced in Brattleboro, Vermont from 1965 to 1970, and then located in Belfast where he is affiliated with the Waldo County General Hospital.

Dr. Knuuti is a member of the Waldo County Medical Society and the Maine Medical Association.

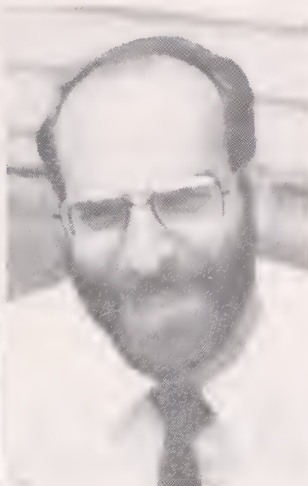
DR. SWENGEL of North Leeds was born on May 28, 1934 in Grandisland, Nebraska, son of Elmer M. and Francis L. Swengel. He was graduated from Kansas State College and received his medical degree from the University of Kansas School of Medicine in 1960. Dr. Swengel served in the U.S. Navy as a Lieutenant Commander from 1959 to 1964, interned at the U.S. Naval Hospital in San Diego from 1960 to 1961 and served residencies in General Surgery and Neurosurgery at the Yale-New Haven Hospital. He was instructor in Neurosurgery at Yale University School of Medicine from 1968 to 1969. In 1969, Dr. Swengel located in Lewiston where he is on the staff of the Central Maine General and St. Mary's General hospitals.



DR. KNUUTI



DR. SWENGEL



DR. NICHOLAS



DR. BOSTWICK

He is also on the hospital consulting staffs of the Bath Memorial in Bath, the Franklin County Memorial in Farmington, the Regional Memorial in Brunswick, the Stephens Memorial in Norway and the Veterans Administration Center in Togus.

He is a member of the Androscoggin County Medical Society (and Secretary-Treasurer), the Maine Medical Association, the American Association of Neurological Surgeons, the Maine Neurosurgical Society, the Congress of Neurological Surgeons and the New England Neurosurgical Society. Dr. Swengel has been Vice Speaker of the M.M.A. House of Delegates since 1974.

DR. NICHOLAS of Mars Hill was born in Antigonish, N.S., Canada on May 1, 1937, son of Elias and Winnifred Nicholas. He was graduated from Acadia University, received his medical degree from Dalhousie University Faculty of Medicine in 1962, and interned at the Victoria General Hospital in Halifax. In 1962, he located in Fort Fairfield where he was affiliated with the Community General Hospital. Dr. Nicholas has practiced in Mars Hill since 1963 and is affiliated with the Aroostook Health Center.

He is a member of the Aroostook County Medical Society, the Maine Medical Association and the American Medical Association. Dr. Nicholas has been a delegate of the Aroostook County Medical Society to the M.M.A. since 1973, and is a member of the M.M.A. School Health Committee. Several of his non-professional interests include: member of the Aroostook Health Center Board of Directors; Pediatric Nurse Associate Preceptor; Family Practice Physician Preceptor, Eastern Maine Medical Center, Bangor; Physician Advisor to Blaine Head Start Program; and Physician member, Family Planning Program.

FROM THE SECRETARY'S NOTEBOOK — *Continued from Page 240*

activities of the Committee for a Medical School for Maine. Members now include physicians, legislators and lay persons. The Committee intends to continue its efforts to advance the cause of a school in any way which seems appropriate, Dr. Robertson said.

Certificate of Need — Dr. Swengel spoke briefly on this proposed legislation (which all delegates had a copy of) and urged all to read it carefully and talk to legislators about it.

Special Memberships — The recommendations for special memberships were *approved*, with one

additional name — Dr. John F. Dougherty of Bath for Affiliate status.

Stenographic Record — A summary of the proceedings of the House of Delegates is being sent to the county presidents, and to the members of the House of Delegates. (The complete report is on file in the Association's office in Brunswick, where it is available to any member of the Association.)

The meeting was recessed at 4:20 P.M. on Saturday, June 5; and adjourned at 5:10 P.M. on Sunday, June 6.

PATRICIA A. BERGERON
Secretary-Treasurer, M.M.A.

Clinical Use of Oral Hypoglycemic Agents — 1976

SIGRID A. HAGG, M.D.

ABSTRACT

This article reviews the pharmacology, indications, interactions and clinical effectiveness of oral hypoglycemic agents. The use of these agents is discussed in view of the findings of the University Group Diabetes Program study. It is concluded that oral hypoglycemic agents, in conjunction with diet and weight reduction, may be useful in selected patients, but that insulin is preferable in most instances.

Oral hypoglycemic drugs have been widely used in the treatment of maturity-onset diabetes since they were introduced 20 years ago. After publication of the findings of the University Group Diabetes Program (UGDP),^{1,2} use of these agents temporarily declined but quickly resumed their steady expansion.³ The UGDP report brought attention to the lack of basic information on the mechanism of action and toxic effects of the oral hypoglycemic agents and led to a thorough reevaluation of the indications for their use. These drugs have had a high degree of patient acceptance because they relieve the clinical symptoms related to hyperglycemia and obviate the need for daily insulin injections. At times this has led to an inadequate emphasis on diet and weight reduction, which are central to the treatment of maturity-onset diabetes. It is the purpose of this review to summarize the clinical use of the oral hypoglycemic agents based on current understanding of their hazards and possible benefits in selected patients.

THE UGDP STUDY

Begun in 1957, the UGDP study was a prospective clinical evaluation of oral hypoglycemic agents. Patients with recent diagnosis of maturity-onset diabetes, i.e., those most likely to respond to oral agents, were randomly assigned under double-blind conditions of one of four treatments: placebo, fixed-dose tolbutamide (1/5 g/day), fixed-dose insulin calculated for body surface area, or variable-dose insulin to approximate normoglycemia. Later,

a fifth group treated with phenformin (0.1 g/day) was added. The results of the study were unexpected. Blood glucose was controlled only in the variable insulin group. Cardiovascular deaths occurred more than twice as often among phenformin and tolbutamide recipients than among patients treated with insulin or placebo. Significant increases in heart rate and in systolic and diastolic blood pressure were also noted in the phenformin-treated group. In addition, after eight years of follow-up, no evidence was obtained that control of blood glucose levels was effective in delaying or preventing diabetic vascular complications. These findings stimulated debate for and against the use of oral agents.^{4,6} Satisfactory answers to some of the questions raised will require further research. For example, the possibility remains that baseline variations between the treatment groups in age, blood glucose, cardiovascular risk factors, and concurrent use of other drugs, each not statistically significant, may have had a cumulative influence on cardiovascular mortality. Non-fatal cardiovascular events were not compared. Data on risk factors such as cigarette smoking were not obtained. In addition, the fixed-dose regimen, which was necessary for the double-blind design, is not customarily used by practicing physicians. Despite these and other objections, the UGDP study remains the most extensive prospective trial of oral agents available. After careful review of the shortcomings of the UGDP study, the Biometric Society⁷ concluded that baseline differences between the groups could not account for the increase in cardiovascular mortality observed.

Additional retrospective clinical studies have failed to resolve the issue of the safety of the oral agents. In a study of 2,500 patients at the Joslin Clinic,⁸ no increase in cardiovascular mortality was noted. However, a later review of the Joslin series, after correcting for risk factors, revealed increased death rates for patients treated for more than five years with oral hypoglycemic agents.⁹ In a study of 186 patients with newly diagnosed adult onset diabetes, patients treated with oral agents had an increased frequency of myocardial infarction (19.7%) compared with those treated with diet alone (9.5%).¹⁰ In another study of 184 diabetics admitted to a coronary care unit over a six-year period,¹¹ patients who were receiving oral agents

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TABLE 1

PHARMACOLOGICAL CHARACTERISTICS OF AVAILABLE ORAL HYPOLYCEMIC COMPOUNDS

Drug	Dose (Min-Max)	Duration of Action (hr)	Unit Dose	Time of Peak Concentration After Oral Dose (hr)	Half Life (hr)	Dose Frequency	Price Per 100 Dose Units
<i>Sulfonylureas</i>							
Tolbutamide (Orinase®)	0.5-2.0 g	6-12	0.5 g	3-5 hrs	5-6	Divided	\$ 7.88/C
Chlorpropamide (Diabinese®)	0.1-0.5 g	24-60	0.25 g	4-6 hrs	35	Single	9.54/C
Acetohexamide (Dymelor®)	0.25-1.5 g	12-24	0.25 g	2 hrs	1-2	Single or Divided	4.07/C
Tolazamide (Tolinase®)	0.1-1.0 g	6-18	0.25 g	4-6 hrs	7	Single or Divided	10.98/C
Glibenclamide	2.5-30 mg	15	—	4 hrs	5-7	Single	—
<i>Biguanides</i>							
Phenformin	50-200 mg	4-6	25 mg	2-4 hrs	3	Divided	3.60/C
Phenformin-TD	50-150 mg	8-12	50 mg	—	—	Single or Divided	8.66/C

or insulin had similar mortality rates, despite the higher incidence of retinopathy and preexisting cardiovascular disease (angina, hypertension, and heart failure) in the insulin-treated group. Patients on oral therapy also had an increased incidence of ventricular arrhythmias compared with those on diet or insulin. Keen and coworkers¹² have reported data indicating no toxic effect of tolbutamide; however, this trial is still in progress and the results must be considered preliminary. After review of the available data, the Biometric Society concluded that the findings of these studies generally supported the conclusions of the UGDP study.⁷

PHARMACOLOGIC PROPERTIES AND MECHANISMS OF ACTION

The oral hypoglycemic agents comprise two groups: the sulfonylureas and the biguanides. Their important clinical properties and doses are shown in Table 1. Dosage in excess of the maximum listed rarely increases drug effectiveness.

Sulfonylureas

All sulfonylureas acutely lower blood glucose by inducing insulin release from the pancreas. They are ineffective in patients who lack endogenous insulin. However, in patients receiving chronic therapy, insulin concentrations return to pretreatment levels while the blood glucose lowering effect persists.¹³⁻¹⁵ Tolbutamide restores the responsiveness of the pancreas to subthreshold levels of glucose, suggesting that it acts to enhance insulin release.¹⁶ An alteration in the kinetics of insulin release, or a decrease in glucagon levels,¹⁷⁻¹⁹ may explain the improved glucose tolerance in patients receiving chronic sulfonylurea therapy.

The therapeutic effects of sulfonylureas may also be related to the extrapancreatic actions of these drugs. Tolbutamide potentiates the action of insulin on skeletal muscle glucose transport. Tolbutamide also potentiates the effects of insulin on

the liver, as well as having a direct effect on hepatic gluconeogenesis.²⁰ Sulfonylureas may enhance insulin binding to tissue receptors thereby increasing insulin effectiveness.

The sulfonylureas are rapidly absorbed after oral administration and are hydroxylated in the liver to active and inactive metabolites that are almost totally excreted in the urine.²¹ Chlorpropamide was initially thought to be largely excreted in the urine without metabolic alteration,²² but recent evidence suggests that up to 80% of the drug may undergo metabolic transformation.²³ Much of the activity of acetohexamide is due to its metabolic product, hydroxyhexamide, which has a half-life two to three times that of the parent compound.²⁴ Sulfonylureas are largely bound to plasma proteins²⁵ and are distributed in the extracellular space.²⁶

The duration of action of these drugs is not necessarily related to drug half-life or serum level.²¹ Variable factors such as protein binding, hepatic inactivation, tissue levels, and excretion, all influence the duration of action and the rates of disappearance from serum. Extrapancreatic effects may also vary in different clinical circumstances. Tolbutamide, because of its metabolism mainly to inactive products by the liver, may be safer than other sulfonylureas in patients with renal insufficiency. In therapeutic doses all sulfonylureas are equally effective in lowering blood glucose. Choice of a particular agent depends on the experience of the physician and the cost and convenience for the patient. Less frequent dosage usually yields better patient compliance.

Biguanides

Phenformin is the only biguanide available in this country. It is effective in lowering blood glucose in diabetic patients, but has no hypoglycemic effect in normal man.²⁷ Lower basal and stimulated insulin levels occur with phenformin treatment, probably due to its glucose-lowering ac-

TABLE 2

DRUGS THAT MAY INTERACT WITH SULFONYLUREA HYPOLYCEMIC AGENTS

Drug	Interaction
Alcohol	Have additive hypoglycemic effect
Salicylates	
Dicumarol	
Chloramphenicol	
Phenylbutazone	
Sulfonamides	Increase duration of action or serum levels of sulfonylureas; may cause hypoglycemia
Thiazides	
Monoamine oxidase inhibitors	
Propranolol	
Oral contraceptives	
Glucocorticoids	Promotes peripheral insulin resistance; may cause hyperglycemia
	Promotes peripheral insulin resistance and enhances gluconeogenesis; may cause hyperglycemia

tion.²⁸ The drug appears to act at multiple sites, producing decreased hepatic gluconeogenesis, inhibition of oxidative enzymes with increased anaerobic glycolysis, and decreased glucose absorption from the small intestine.²⁹ Phenformin has been used to treat hypoglycemia due to rapid intestinal glucose absorption³⁰ and has been suggested as a preferred treatment for the obese diabetic because of its anorexogenic effect.³¹

Phenformin is inactivated in the liver by hydroxylation. Both the metabolites and the active drug are excreted in the urine.³² About two-thirds of phenformin appearing in the urine is non-metabolized;³² this may account for increased drug toxicity in patients with impaired renal function.

HAZARDS AND SIDE EFFECTS OF ORAL HYPOLYCEMIC AGENTS

The increase in cardiovascular mortality during treatment with sulfonylureas or biguanides is the unwanted effect to be considered in prescribing these medications. The relationship of the toxic effects to the therapeutic actions of the drugs is an area of continuing study. Hypoglycemic agents for which toxic and therapeutic effects can be dissociated are being actively sought.

Reversible side effects have occurred in less than 5% of patients receiving sulfonylureas.³³ Common side effects include nausea and skin rash. Because of its long half-life, chlorpropamide may produce problems of drug accumulation; it has been associated with hypoglycemia, especially in elderly patients.³⁶ Toxicity due to sulfonylureas includes cholestatic jaundice, although alterations in liver function may also occur with poorly controlled diabetes. Blood dyscrasias, such as transient leukopenia, agranulocytosis, or fatal aplastic anemia, have occurred,³³⁻³⁵ but appear to be rare. Sulfonylureas have a goitrogenic effect in animals and man, but this is rarely of clinical importance.³⁷ Chlorpropamide, and occasionally tolbutamide, may produce dilutional hyponatremia, both by enhancing the release of antidiuretic hormone (ADH) from the posterior pituitary and by increas-

ing renal tubular sensitivity to ADH.^{38,39} Sulfonylureas may cause severe nausea and vomiting after alcohol ingestion; this disulfiram-like effect may occur in 10% of patients taking chlorpropamide, but is less common with the other sulfonylureas.⁴⁰ In therapeutic concentrations, sulfonylureas activate adenylyl cyclase in human cardiac muscle, and have a positive inotropic effect on animal but not human cardiac muscle.⁴¹

Side effects are common with biguanide therapy, occurring in about 60% of patients. The most frequent symptoms are gastrointestinal; and include a metallic taste, anorexia, and nausea; these effects often require discontinuation of therapy.³ Lactic acidosis in association with biguanide therapy is probably due not only to the drug but also to its use in susceptible patients, particularly those with renal insufficiency in whom drug accumulation may be excessive.⁴² Phenformin has been implicated as a cause of pancreatitis and asymptomatic increases in urine and serum amylase.^{43,44} Biguanides have no effect on adenylyl cyclase in cardiac muscle.⁴¹

DRUG INTERACTIONS

Sulfonylureas interact with many commonly used drugs¹⁸ (Table 2). Alcohol and salicylates, because of their direct hypoglycemic activity, may precipitate hypoglycemic coma in patients receiving sulfonylureas.⁴⁷ Propranolol, by interfering with glycogenolysis and glucagon release, may enhance the hypoglycemic action of the sulfonylureas.⁴⁸ Propranolol may also interfere with glucose-induced insulin release, leading to hyperglycemia, particularly in patients with decreased insulin reserve.⁴⁹ Thiazide diuretics interfere with insulin release, possibly because of tissue depletion of potassium.^{45,46} Oral contraceptives and glucocorticoids produce peripheral insulin resistance; the latter also enhance gluconeogenesis. Certain drugs may influence the absorption, metabolism or excretion of sulfonylureas. Dicumarol, sulfonamides, chloramphenicol, and phenylbutazone appear to increase circulating tol-

butamide concentrations and prolong the half-life of the drug in man.^{47,50} These drugs displace sulfonylureas from human serum albumin,⁵¹ although this may not be the sole mechanism for the enhanced hypoglycemic effect. They also interfere with the hydroxylation of sulfonylureas, which is probably rate-limiting for their metabolism in the liver.¹⁸ Phenylbutazone inhibits the renal excretion of hydroxyhexamide, the active metabolite of acetohexamide.⁵²

Ethanol potentiates the effect of phenformin to decrease lactate utilization in man.⁵³ Other drug interactions of the biguanides remain unexplored.

CLINICAL USE OF THE ORAL HYPOGLYCEMIC AGENTS

The appropriate use of the oral hypoglycemic agents rests on the initial diagnosis of diabetes. Mild to moderate diabetics, classified by the criteria of Fajans and Conn,²⁷ are most likely to achieve adequate blood glucose lowering with therapy. Complete normalization of blood glucose is rarely possible. Despite suggestive evidence from animal studies,^{54,55} conclusive proof is lacking that control of blood glucose delays or prevents vascular complications of diabetes in humans. However, control of blood glucose relieves the annoying symptoms of hyperglycemia and many reduce the incidence of certain infections of the genitourinary tract.⁵⁶

Physicians should establish definite criteria for control. At the Joslin Clinic, control is assessed by measurement of fasting and three-hour postprandial blood glucose values. Control is considered to be good if 70% of whole blood glucose values are less than 110 mg/100 ml, and fair if less than 130 mg/100 ml. All others are considered to be poorly controlled.⁵⁷ Corresponding values for serum or plasma are 15% higher. These figures are somewhat arbitrary, but provide a reference point for clinical decision-making.

Doubts about the long-term safety of the oral hypoglycemic agents have led to increased emphasis on diet. Many studies have shown the effectiveness of diet therapy in maturity-onset diabetes; the degree of response is usually related to the degree of successful weight reduction. Diabetes is worsened by obesity because of peripheral insulin resistance. Weight reduction improves glucose tolerance and may also induce recovery of islet cell function. In a recent study of 118 patients with mild maturity-onset diabetes, two months of dietary treatment resulted in adequate control of blood glucose in 59% and improved glucose tolerance in almost all patients.⁵⁸ Despite the demonstrated effectiveness of diet therapy, relatively few patients understand and adhere to an appropriate diet. Although there is no simple remedy for this situation, an approach to the problem has been presented.⁵⁹

When diet and weight reduction are ineffective or not feasible, clinicians much choose between

insulin and oral agents. The UGDP study demonstrated that insulin is the safer and more effective approach to control of blood glucose. Most authorities would withhold full approval of the oral agents; the decision to use them still rests with the individual patient and physician. Patients should be informed of the potential risks and should participate in the decision to use these medications.

In patients who are unwilling or unable to use insulin, oral agents may be employed with the aim of controlling the blood glucose. These drugs are most likely to be effective in maturity-onset diabetic patients over 40 years old with diabetes of less than 10 years duration, who can be controlled on less than 20 units of insulin per day. Oral hypoglycemics are contraindicated in ketosis-prone patients or in insulin-dependent juvenile-onset diabetics. The drugs should never be used in ketoacidosis or in patients during pregnancy, surgery, stress or infection. They may lead to severe toxic effects in the presence of cardiac, renal or hepatic disease.

Therapy is initiated using the minimum effective dose and increasing this at weekly intervals until the desired degree of control is reached. Patients who fail to respond to maximal doses within one month are considered to have primary failure, although some individuals may respond following weight reduction or a period of insulin therapy. Secondary failure refers to those patients who respond initially but develop hyperglycemia later. Many of these patients may not be adhering to instructions for diet or weight reduction or may be under metabolic stress. The rate of secondary failure is estimated to fall between 3 and 10%.⁶⁰ Most patients who are not controlled on sulfonylureas or phenformin alone will respond to concurrent use of both. However, since indications for use of either of these drugs are now more limited, combination therapy should be considered the last and least attractive alternative.

In patients who initially or subsequently are not controlled on oral agents, daily injection of insulin is indicated. Evaluation may be difficult because of the cyclic nature of the disease. During stable periods, oral agents or insulin in doses less than 20 units per day may control the blood glucose, while at other times oral agents may be inadequate and higher doses of insulin required. Insulin clearly offers greater flexibility in the treatment of such cases.

At present it is not established whether the UGDP findings apply to sulfonylureas other than tolbutamide. Rational therapy will depend on improved understanding of factors influencing drug toxicity as well as the onset and progression of diabetic vascular disease. Administration of oral hypoglycemics to asymptomatic patients does not appear to be rational on the basis of current knowledge.

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Drug Utilization Review is part of the Medicaid drug program in your state. The goal is to assist in the delivery of rational drug therapy for Medicaid patients and reduce the over all cost of the Medicaid drug program.

How can Drug Utilization Review do that?

It is done by reviewing Medicaid drug use and sharing the results of the review with those doctors and pharmacists involved in treating the patient. When a Medicaid prescription claim is processed, a computer records who received the drug, who prescribed it, who dispensed it, and what kind of drug it was. Once a month, the computer compares the drug use records of each patient with several criteria, such as kinds of drugs used, amounts purchased, number of doctors visited, and so on.

When a patient's drug use goes beyond any of the criteria, the computer prints a report for review by the Drug Utilization Review Committee.

Just who is the Drug Utilization Review committee?

It is a group of fellow health care professionals—physicians and pharmacists from your area. Committee members are selected from nominations made by your local medical and pharmaceutical associations. Each member serves for 1 to 3 years. You may be invited to serve on the committee at some time.

What does the Drug Utilization Review committee do?

The committee reviews patient drug histories showing drug use patterns which exceed criteria set for the program. If the questionable pattern appears to be minor or temporary, the committee may decide to take no further action.

If the situation is more serious, the committee will write to the doctors and pharmacists involved to advise them of the potential problem. For example, the records might show that a patient is going to several doctors to get prescriptions for the same drug. The committee would advise each of the doctors of this practice. In another case, the committee might recommend that a doctor prescribe maintenance drugs in larger, more economical quantities, if the patient's condition warrants it.

Are you trying to tell me how to treat my patients?

Not at all. Your patients' treatment is in your hands, where it belongs. All Drug Utilization Review does is give you information about your patients' drug use that hasn't been available before. The committee can't dictate the kind of drug therapy you use, and wouldn't want to if it could.

What do I have to do if I get a letter about a patient?

The committee will ask you to review your records to see if the situation described in their letter is with your knowledge and conforms with your diagnosis and treatment. If so, please advise the committee of your diagnosis and treatment plan so they'll know that the drug use is appropriate and won't send additional letters in the future.

If the situation is not called for by your treatment plan, the committee asks that you review the situation and make those changes you feel are necessary. In all cases, they try to make it as easy as possible for you to respond to the committee and use the information provided.

How can a physician find out more about the Drug Utilization Program?

A pamphlet which explains the Drug Utilization Review program in detail is available or a visit to your office by a staff member can be arranged upon request. A speaker or a color/sound film can also be provided for local medical societies or other groups interested in further information about the program. Your peers who are members of local peer review committees will be glad to explain the program personally or answer any questions. If you will write or call PAID Prescriptions, any information requested will be provided including the names of committee members in your local area.



PAID PRESCRIPTIONS
One Community Drive
Augusta, ME 04330



WHY WORK-RELATED CLAIMS ARE DENIED

Our Professional Relations representatives receive many questions from participating physicians regarding Blue Shield coverage. In this column we will attempt to answer those that deal with broad policy questions and that would seem to be of interest to most physicians' offices. We would welcome any suggestions for questions you would like to see addressed in this space.

A Worker's Compensation exclusion appears in both Blue Cross and Blue Shield contracts. The Blue Shield exclusion reads: "This Agreement does not include payment for treatment of occupational injuries or diseases for a period for which the employer is required to furnish, pay or provide reimbursement for, in whole or in part; Surgical, Medical, Obstetrical, or Related services or expenses under the provisions of any law of the United States or any state or political subdivision thereof; or for a period for which such service, payment or reimbursement may be obtained by the Member under such laws, even though he waives or fails to assert his rights thereto. This Contract is not in lieu of and does not affect any requirement for coverage by Workmen's Compensation Insurance."

Since we are not a casualty company, we cannot pay Worker's Compensation claims, and we have been taking steps to ensure that any claim that might be work-related is processed properly.

The claims investigation section uses the diagnosis on the claim, the individual's type of employment, and, if warranted, a questionnaire to the individual, to determine whether or not an injury or illness may be work-related and eligible for Worker's Compensation.

While injury due to work-related accidents is relatively simple in terms of applicability to Worker's Compensation, work-related illness is not, and physicians and hospitals alike have become concerned over claims being held up or denied over an illness which might not seem to have a relationship to work.

To understand why we might seem to be over-zealous in investigating work-related illnesses, you must first realize that the definition of such an illness is very broad. According to paragraph 183 of the Maine Workmen's Compensation Act and Occupational Disease Law, an occupational disease "shall be construed to mean only a disease which is due to causes and conditions which are characteristic of a particular trade, occupation, process or employment and which arises out of and in the course of employment."

Once we have determined that a claim may be work-related, we deny payment on the claim. *This decision is reversed*, however, if we receive a denial of Worker's Compensation benefits from the Worker's Compensation Insurance carrier.

One way the entire procedure could be speeded up is to determine whether or not an accident or illness is work-related at the point of service. Even with illness, if this question were asked routinely, some of our investigation time could be diminished and claims might be processed more rapidly as a result.

The point with Worker's Compensation is that the law affords no room for compromise. We are making every effort to ensure that we are not paying claims which are eligible under Worker's Compensation, and we ask for your help and forbearance in this matter.

News, Notes and Announcements

Symposium on Insect Allergy Pan American Medical Association and Florida Allergy Association October 24-29, 1976

Dr. Claude A. Frazier, an allergist from Asheville, North Carolina will be conducting a one-half day symposium on the subject of insect allergy at the combined meeting of the Pan American Medical Association and the Florida Allergy Association. This symposium is scheduled for October 26, 1976 from 2:00 until 5:00 P.M. at the Diplomat Hotel in Hollywood, Florida. This meeting is scheduled for the week of October 24-29, 1976.

Some of the various aspects of insect allergy that will be covered in this symposium are: "Allergic Reactions to Insect Stings, Including the Fire Ant;" "Allergic Reactions to Insect Bites;" "In Vitro Diagnosis and Identification of Insect Allergens;" "Methods of Prevention;" "Toxicology of Venoms;" "Pesticides;" "Immunology of Venoms;" "Hyposensitization."

American Society of Contemporary Medicine and Surgery

The Twelfth Annual Scientific Assembly of the American Society of Contemporary Medicine and Surgery will be held January 30-February 5, 1977 at the Diplomat Hotel in Hollywood, Florida.

The program includes seminars and tutorials on Cardiovascular Disease, Hypertension, Cancer, Infectious Disease, Cryosurgery, Nutrition/Alimentation, Special Medicine and Surgery, Genitourinary Disease, Pulmonary Disease — and other important subjects.

The Permanent Faculty of 100 leaders of American medicine is headed by the ASCMS president, Dr. Michael DeBakey, Chairman Dr. Morris Fishbein, and Vice-Chairman Dr. Leon Jacobson.

This Continuing Medical Education activity meets the criteria for 40 hours of credit in Category I for the Physician's Recognition Award of the AMA and for the Certificate of Advanced Medical Studies of the ASCMS. For information, write: Dr. John Bellows, 30 N. Michigan Ave., Chicago, IL 60602.

County Society Notes

York

The March meeting of the York County Medical Society was held at the H. D. Goodall Hospital, Sanford, Maine on March 10, 1976.

The program was as follows: Social Hour from 6:30 p.m. to 7:30 p.m., Dinner at 7:30 p.m. with speaker and business meeting to follow. It is worthy of mention that the Social Hour was in the hands of Drs. Richards and Vachon. They did their usual magnificent job.

Following an excellent dinner, Dr. Owen O. Dow, President of the York County Medical Society, introduced the featured speaker of the evening, who was Dr. Robert E. McAfee, Surgical Staff of the Maine Medical Center and Mercy Hospital, Portland, Maine. He is also the Delegate from the Maine Medical Association to the American Medical Association. His subject was "Issues of Importance to Medicine" (Need for Increased Membership in Organized Medicine, etc.) He gave an inspiring talk and laid this subject on the line. He was deluged with many questions of vital importance.

Dr. Dow presided over the business meeting. In the interest of time, the minutes of the last meeting were dispensed with. The question of how many credits from Category I should be necessary to meet the Postgraduate Educational requirements of the Maine Medical Association was brought up. It was suggested at the previous meeting of the York County Medical Society that members of our Society write me on their ideas regarding this, but no one did.

The next item on the agenda was the application of Dr. Mirle Kellett, a radiologist for the York and Goodall hospitals, to membership in our Society. He was unanimously elected.

The next meeting of the York County Medical Society was announced and is to be held at the Webber Hospital, Biddeford on Wednesday, May 12, 1976 with the usual format. The President said he would appoint a committee to arrange for this meeting. He also announced the Interim Meeting of the House of Delegates of the Maine Medical Association to be held at the Eastern Maine Medical Center in Bangor, Maine on Saturday, April 3, 1976.

We had planned to have Dr. Robert F. Ficker present a report of a previous Executive Committee meeting of the Maine Medical Association and make a few other remarks; however, he had to leave the meeting by way of necessity and his presentation was turned over to Dr. Roger J. P. Robert.

Dr. Dow also mentioned that a letter had been received from the American Medical Association concerning the participation of our Society in National Health Week. He stated that this letter was so late in arriving that there was insufficient time to prepare for it. He also mentioned that copies of the Legislative Document may be obtained from the Maine Medical Association, P.O. Box 250, Brunswick, Maine 04011. Dr. Maurice Ross stated that it had been voted on to have the secretary send a copy of it to each member of the Society. This was not done because as Dr. Carl Richards had said, this letter is sent out and arrives after the business for that week is transacted. If you are interested, you can get all this information from the morning edition of the Portland Press Herald.

The correspondence from Dr. Manu Chatterjee concerning Medical Assistants was brought up and Dr. Dow mentioned the date of such a meeting to be held in Portland, Maine at the Maine Medical Center and that it was open to anyone who wished to attend. In addition, a letter from Dr. David Reed concerning Hearing Aid Devices was discussed in brief. Meeting was adjourned!

I would be remiss if I didn't mention the letter sent to each member in the county regarding attendance at this meeting. This was sent to non-members as well. There were 36 present including physicians and guests. This was truly a great meeting. I am sorry to say that those who didn't attend missed the boat, including a delicious meal.

MELVIN BACON, M.D., *Secretary*

Kennebec

The Council of the Kennebec County Medical Association met with delegates to the Maine Medical Association at the Holiday Inn in Augusta, Maine on May 5, 1976, for the purpose of discussing the resolutions that would be coming up. Other business that was discussed included: 1.) A request from Mrs. Jafar Chafi for a contribution to the Auxiliary for the Health Career Scholarship Program. The council voted to donate \$500.00 for that purpose. 2.) Two complaint letters were received, both of which were discussed and felt to require no further action at the present time. 3.) A letter having been received from the Secretary of the Aroostook County Medical Society regarding the standing of Dr. Douglas Collins; he was accepted into full membership in the Kennebec County Medical

Association. 4.) The correspondence from Mrs. Bergeron regarding Dr. Nikolaidis' request for a non-active membership status was read. The Council felt that there was no provision for this type of membership in the Bylaws and that Dr. Nikolaidis would simply have to either pay the dues or become an inactive member. The remainder of the meeting was devoted to a free discussion of a variety of subjects. No actions were taken at this time specifically.

O. THOMAS FEAGIN, M.D., *Secretary*

Aroostook

A meeting of the Aroostook County Medical Society was held on March 31, 1976 in Presque Isle, Maine.

It was voted to recommend Dr. Gordon Johnson for affiliate membership and to transfer Dr. George J. Harrison to active membership.

The following physicians were elected to membership in the Aroostook County Medical Society: Drs. William H. Nestler, Fort Fairfield, Lawrence Goloduer, Caribou, Paul A. Nicholas, Fort Kent and Herman A. Wallinga, Presque Isle.

GEORGE J. HARRISON, M.D., *Secretary*

Cumberland

The 404th meeting of the Cumberland County Medical Society was held at the Red Coach Grill on May 20, 1976. Eighty-five members were present.

Reading of the minutes of the previous meeting was dispensed with.

A Treasurer's report was given. It was announced that dues next year would probably not be raised.

Correspondence and Applications for Membership

Final reading of applications on Drs. Omar D. Crothers, III and Edward R. Nowicki resulted in a vote to accept these physicians as members of the Cumberland County Medical Society.

Unfinished Business

Resolutions were read on the deaths of Drs. Adrian H. Scolten and Francis X. Mack. Comments were made upon the subject of consumer and professional directories.

New Business

Dr. William J. Hall, III addressed the membership on the matter of "Swine Influenza."

A resolution was introduced by Dr. Robert True suggesting the Society donate a sum of money to the Primary Medical Care Center to be formed on the West end peninsula. After a number of parliamentary maneuvers, it was concluded a special meeting would have to be called to approve the sum of money suggested.

The site for the September Annual Outing of the C.C.M.S. was unanimously agreed upon as the Homewood Inn.

Dr. Robert E. McAfee announced that a special caucus of the delegates to the June meeting in Rockport would be called within the next week or so.

The Ethics and Discipline Committee reported on four cases reviewed within the past year.

At the close of the meeting the annual election of officers took place with the following results:

President: Dr. Robert E. McAfee, Portland
Vice-President: Dr. Clement A. Hiebert, Portland
Executive Committee: Dr. William H. Maxwell, Portland
Professional Ethics Committee: Dr. John E. Knowles, Portland

Delegates to the M.M.A. House of Delegates (2 yrs.): Drs. Louis A. Ciampi, Patrick A. Dowling, Andrew P. Iverson, Jr. and John D. Kilgallen, all of Portland, Harold N. Burnham, Gorham and Raphael F. Turgeon, Westbrook. Alternates (2 yrs.): Drs. Carl A. Brinkman, Brian M. Dorsk, John A. Godsoe, Michael L. Shuman and Peter B. Webber, all of Portland, and Stephen B. Paulding, Cumberland Foreside.

The meeting adjourned at approximately 9:50 p.m.

WESLEY J. ENGLISH, M.D., *Secretary*

Oxford

The annual Spring meeting of the Oxford County Medical Society was held on May 26, 1976 at the Rumford Community Hospital at 6:00 p.m.

There were twenty members and one guest attending. The meeting was called to order and presided over by the President, Dr. Adwaita K. Ganguli.

The minutes of the previous Fall meeting were read and accepted. The Treasurer's report was given.

Old Business: There was none.

New Business: The status of this County Society and its future was discussed. Many participated and commented; it seemed to be the consensus of the membership to continue the Society rather than to disband or join another county at the present time. It was also voted on motion to increase the number of meetings per year to four, two of these to be related temporarily to the Spring and Fall House of Delegates Meetings. It was also moved to include some Category I, CME content to at least one of the meetings and to appoint a Program Committee.

An item-by-item discussion of all the upcoming resolutions before the House of Delegates was held and the instruction in the affirmative for all resolutions was given to the delegates and alternates.

Dr. Sidney M. Schnittke volunteered to assume the vacated Office of Secretary-Treasurer and this was accepted. Dr. Ganguli indicated that he would appoint Nominating and Program Committees to prepare for the next meeting.

Meeting was then adjourned to the cafeteria, where again a rather gracious meal was enjoyed.

DAVID L. PHILLIPS, M.D., *Acting Secretary*

Franklin

The Franklin County Medical Society meeting was held on June 7, 1976.

The President, Dr. Paul Brinkman called the meeting to order.

Report of Maine Medical Association, House of Delegates June meeting given by Drs. Daniel K. Onion and David C. Dixon:

1. Special emphasis on malpractice resolution.
2. Assistant Executive Director of the State Association.
3. New Fifth District representative, and communications problems with the outgoing representative on the Executive Committee of the State Association.
4. Invitation by Dr. N. Burgess Record, Jr. to all primary care members of the Society to attend an organizational meeting of a foundation-like group of providers to provide health care to a prepaid health plan.

DANIEL K. ONION, M.D., *Secretary*

DRUG THERAPY REVIEWS — CLINICAL USE OF ORAL HYPOGLYCEMIC AGENTS — 1976

Continued from Page 250

58. Doar, J. W. H., Wilde, C. E., Thompson, M. E., et al: Influence of treatment with diet alone on oral glucose tolerance test and plasma sugar and insulin levels in patients with maturity-onset diabetes mellitus. *Lancet* 1: 1263-1266, 1975.
59. West, K. W.: Diet therapy of diabetes: An analysis of fail-

- ure. *Ann Intern Med* 79: 425-434, 1973.
60. Krahil, L. P.: The clinical use of oral hypoglycemic agents. In *Diabetes Mellitus: Theory and Practice*. Edited by M. Ellenberg, H. Rifkin. New York, McGraw-Hill Book Company, 1970, pp 648-673.



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Drug Therapy Reviews

Russell R. Miller, Pharm.D., Ph.D. and
David J. Greenblatt, M.D., Editors

Pharmacotherapy of Asthma

MILES WEINBERGER, M.D. and LESLIE HENDELES, Pharm.D.

ABSTRACT

Asthma is a complex disease of unknown etiology and highly variable clinical presentation that is characterized by hyperreactive airways. A proliferation of pharmaceutical preparations has resulted in therapeutic confusion. Drugs of proven value for asthma are of four types: (1) phenylethylamine sympathomimetics (2) theophylline preparations (3) cromolyn sodium and (4) corticosteroids. The sympathomimetics and theophylline are bronchodilators; corticosteroids are anti-inflammatory agents; and cromolyn is purely a prophylactic agent having no anti-inflammatory or bronchodilator properties. The sympathomimetics are most effective as parenteral or inhaled agents for the relief of acute symptoms. Theophylline and cromolyn are effective and safe for long-term suppressive therapy. Corticosteroids administered on a daily basis are the most potent medications for controlling severe asthmatic symptoms. Short-acting corticosteroids administered orally on an alternate-day basis and new preparations for inhalation have the potential for reasonably safe long-term suppression of disabling chronic disease not adequately controlled by more conservative measures.

INTRODUCTION

The pharmacological management of asthma dates to antiquity. The ancient Chinese herb, Ma Huang, had been used for 4000 years before its active ingredient was isolated and named ephedrine from the western name for the herb, *Ephedrus vulgaris*.¹ This orally effective agent was found to have properties similar to the more potent sympathomimetic drug, epinephrine, which was first reported as a bronchodilator in 1903.² These two agents and the fumes from burning stramonium leaves, which had anticholinergic and probably bronchodilator effects, were the only pharmacologically active substances used for asthma until the introduction of theophylline in the late 1930's.³ Cortisone first was used for the treatment of asthma in 1950,⁴ and the glucocorticosteroids remain the most potent and potentially the most dangerous of anti-asthmatic agents. The number of sympathomimetics⁵ and corticosteroid agents⁶ has increased since the prototypes were first used and a new anti-asthmatic, cromolyn sodium,⁷ has been introduced. Pharmacotherapy for asthma initially was directed primarily against acute symptoms or "attacks." Only more recently has attention been focused on "prophylaxis," i.e., the prevention of daily or frequently recurrent symptoms that restrict normal activities in many patients.

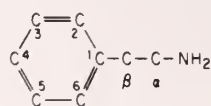
The expanding array of available drugs has increased demands on the pharmacological knowledge of physicians caring for asthmatics. The first part of this review will deal with the pharmacology of these agents. Asthma is sufficiently variable in its presentation and duration of symptoms, however, that an understanding of the pathophysiology and

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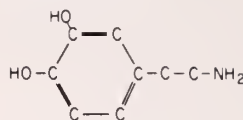
Leslie Hendeles, Pharm.D. is Clinical Pharmacist, Pediatric Allergy Clinic, University of Iowa Hospitals, and Assistant Professor of Clinical Pharmacy, University of Iowa College of Pharmacy.

Address reprint requests to Dr. Weinberger at the Department of Pediatrics, University of Iowa Hospitals, Iowa City, Iowa 52242.

PHENYLETHYLAMINE



CATECHOLAMINE



Drug Name	Structure	Major Receptor Activity	Oral Bioavailability In Conventional Doses	Approximate Duration Of Effect
NOREPINEPHRINE		α	NO	<1 HOUR
PHENYLEPHRINE		α	NO	<1 HOUR
EPINEPHRINE		α, β_1, β_2	NO	<1 HOUR
EPHEDRINE		α, β_1, β_2 CNS	YES	4 HOURS
ISOPROTERENOL		β_1, β_2	NO	<1 HOUR
ISOETHARINE		β_2	SOME	1 HOUR
METAPROTERENOL		β_2	YES	4 HOURS
TERBUTALINE		β_2	YES	6 HOURS
ALBUTEROL		β_2	YES	6 HOURS

Fig. 1. Structure and function of sympathomimetic amines. The carbon atoms are indicated in the conventional labeling of the basic phenylethylamine structure with numbers used to identify the positions in the benzene ring while α and β identify the positions in the side chain. Adrenergic receptor activity is indicated by the conventional α , β_1 , and β_2 . Pharmacological effects associated with the stimulation of these receptors are indicated in Table 1.

TABLE 1

SELECTED PHARMACOLOGICAL EFFECTS OF SYMPATHOMIMETICS	
Clinical Effect	Receptor ⁸
Bronchodilation	Beta ₂
Tremors	Beta ₂
Tachycardia and arrhythmias	Beta ₁
Hypertension	Alpha
Pallor	Alpha
Urinary retention	Alpha
Central nervous system stimulation	Not defined — dependent upon crossing blood-brain barrier

natural history of the disease is essential for appropriate application of pharmacotherapy. Thus, a final section will attempt to place the various drugs into appropriate therapeutic perspective by relating the clinical pattern and physiology to drug selection.

PHARMACOLOGY OF ANTI-ASTHMATIC AGENTS

Sympathomimetic Amines

The first available sympathomimetic bron-

chodilator drugs, epinephrine and ephedrine, stimulate multiple adrenergic receptors⁸ (Table 1). While both these and subsequently developed drugs in this class are phenylethylamines (Figure 1), most of the newer drugs are not catecholamines (3, 4-dihydroxyphenylethylamines) and therefore do not undergo the rapid inactivation in the gut and lung by catechol-ortho-methyl-transferase (COMT) that is exhibited by epinephrine, isoproterenol, and isoetharine. Further inactivation of these drugs can occur (predominantly in the liver) by monoamine oxidase (MAO). This is diminished by substitution on the alpha carbon atom and perhaps also to some extent by increased size of the N-alkyl substituent. Phenylephrine exemplifies a sympathomimetic with oral requirements 50 fold greater than intramuscular because of rapid metabolism during passage through the gut and/or portal system.⁹ Those agents that avoid significant metabolism by COMT and MAO exhibit more reliable oral bioavailability and increased duration of activity when compared with

the catecholamines.

For parenteral use, a new alternative to epinephrine is terbutaline. Subcutaneous administration of 0.25 mg terbutaline was equivalent in intensity, duration, and side effects to the conventional 0.25 mg dose of epinephrine in one study.¹⁰ Higher doses of terbutaline (e.g., 0.5 mg) result in great efficacy than the conventional epinephrine dose but only at the expense of increased toxicity.¹¹

All of the sympathomimetic bronchodilators other than ephedrine are effective by the inhaled route. Epinephrine is the bronchodilator in non-prescription inhalers (e.g., Primatene mist) and exhibits only very transient effects in the dose used.¹² Isoproterenol (isoprenaline) has been the most commonly prescribed aerosol and is consistently unexcelled in onset and intensity of action though its duration of effect is also brief.¹³⁻¹⁸ Doses that are equipotent with isoproterenol though with less cardiac effect have been demonstrated for terbutaline,¹³ albuterol (salbutamol),¹⁴ and isoetharine¹⁵ while metaproterenol (orciprenaline) appears to be equitoxic if equipotent doses are administered.¹⁴

Terbutaline and albuterol have the longest durations of action (4 to 6 hours) in single dose studies.^{13,19,20} Metaproterenol also has a duration of action longer than isoproterenol^{18,21} though somewhat shorter than terbutaline and albuterol.^{12,19} In a study of chronic metaproterenol usage, its duration of action appeared to decrease from a half-life of 4 hours to 2 hours after 60 days.²¹ In the same study, the half-life of isoproterenol effect decreased from an initial 2 hours to less than 1 hour with chronic dosing. Tolerance has also been demonstrated for some beta receptor effects of terbutaline.²² Isoproterenol, in fact, has been shown to exhibit a paradoxical effect after the initial bronchodilation in some patients receiving multiple daily doses for prolonged periods.²³⁻²⁵ Even normally, the maximal effectiveness of a single dose of isoproterenol passes so quickly that its early impressive blocking of exercise-induced bronchospasm is lost within one hour while albuterol is still effective.²⁶

Isoetharine with phenylephrine (Bronkometer®) has a duration of effect that is intermediate between isoproterenol and the new agents.^{15,16} Published data do not consistently support clinically important prolongation of the effect of the isoproterenol by the addition of phenylephrine (Medihaler-Duo).^{13,27}

Excessive use of high dose isoproterenol inhalers in England (five times the strength of U.S.A. preparations) was associated with an increased frequency of deaths in asthmatics during the late 1960's; the mortality rate declined to normal levels after aerosols were made available only by prescription.²⁸ This observation has stimulated an extensive review of potential toxicity from use of these inhaled drugs.²⁹ Cardiac toxicity from isoproterenol and fluorinated hydrocarbon propellants increases in hypoxic animals; sudden death due to ventricular fibrillation may result. Alternatively, asphyxia may oc-

cur from progressive disease in patients not seeking medical assistance because of falsely reassuring transient benefit from the inhalers.

Metaproterenol, terbutaline, and albuterol have been introduced as orally effective sympathomimetic bronchodilators. (Isoproterenol is also available as an oral preparation, which is not bioavailable, and as a sublingual preparation, which has very limited efficacy.)³⁰ Among these selective beta₂ antagonists, albuterol (4 mg) and terbutaline (5 mg) appear to be equally effective with tremors present in about one-third of patients taking either drug.³¹ One study has reported terbutaline at both 5 and 7.5 mg significantly more effective than metaproterenol at 20 mg³² although another study reported the efficacy of metaproterenol (20 mg) equal to albuterol (4 mg).³³ Additional inconsistencies include other reports indicating that metaproterenol (20 mg)³⁰ and terbutaline (2.5 mg)³⁴ were not more effective than ephedrine and albuterol (4 mg) was less effective than a combination of ephedrine (25 mg), theophylline (130 mg), and hydroxyzine (10 mg).³⁵ This latter preparation is relatively ineffective in managing chronic asthma when compared with theophylline alone in doses that achieve therapeutic serum concentrations.^{36,37}

Since ephedrine alone, in spite of proven bronchodilator efficacy, is relatively ineffective in controlling chronic asthma,^{36,37} additional data are needed to define the role of sympathomimetics as a class for chronic therapy. Terbutaline and albuterol, however, appear to be the most potent of the nonparenteral preparations for acute therapy and the inhaled route of administration probably provides quicker onset of action, greater intensity of effect, and less frequent adverse effects.

Theophylline

Theophylline is a naturally occurring dimethylated xanthine with bronchodilator effect. Other dietary xanthines include its isomer, theobromine, and the trimethylxanthine, caffeine; these agents share the weak diuretic action of theophylline but are not used as bronchodilators.³⁸ The mechanism of bronchodilator action is postulated to be different from that of the sympathomimetic amines (Figure 2). While the sympathomimetic amine beta agonists stimulate adenylyl-cyclase, theophylline inhibits phosphodiesterase. Thus, both may result in accumulation of intracellular cyclic AMP and relaxation of bronchial smooth muscle.³⁹

Theophylline has been marketed in an extensive variety of preparations (Table 2). Some of the most popular are fixed-dose combinations that include other medications such as ephedrine and a sedative. Many include theophylline mixed with a pharmacologically inactive strong base. A stable dihydroxypropyl derivative of theophylline, dyphylline, is also currently marketed in the United States. These various preparations are packaged for parenteral, oral and rectal use. Parenteral preparations are available for intravenous and intramuscular use.

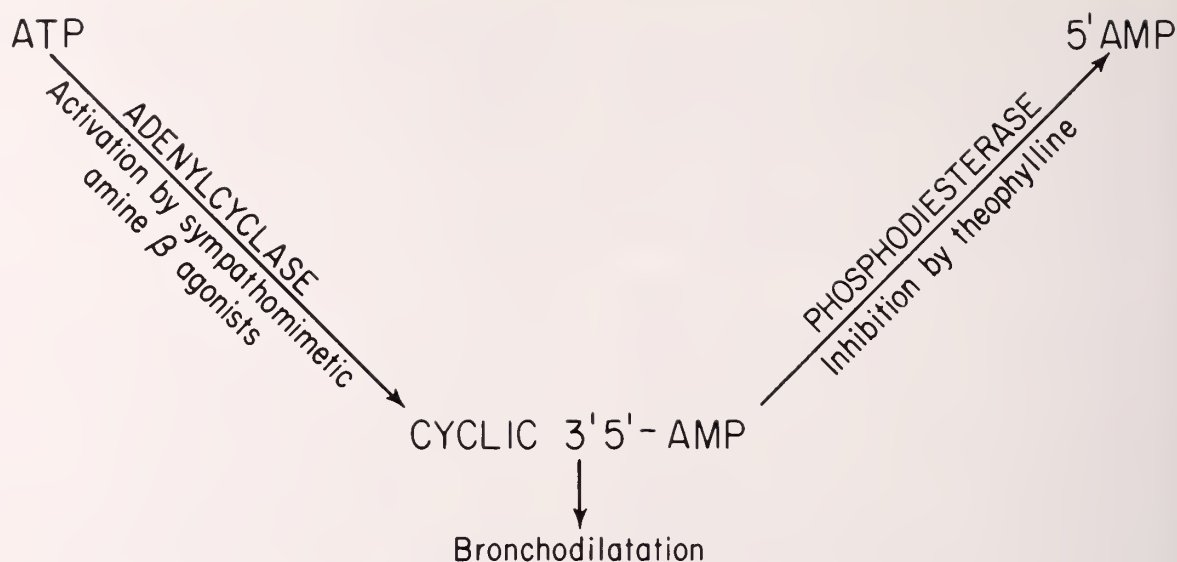


Fig. 2. Postulated mechanism of bronchodilation for sympathomimetic β_2 agonists and theophylline.

TABLE 2

THEOPHYLLINE CONTENT OF MARKETING THEOPHYLLINE PREPARATIONS	
Theophylline N.F.	100%
Theophylline monohydrate N.F.	90%
Aminophylline U.S.P. (theophylline-ethylenediamine)	78-86% ^a
Theophylline monoethanolamine	75%
Oxtriphylline (choline-theophylline)	65%
Theophylline sodium glycinate	50%
Theophylline calcium salicylate	48%
Dyphylline	0% ^b

^aVariability dependent on presence of anhydrous or monohydrated theophylline

^bThis is a stable theophylline derivative that does not yield theophylline in solution or *in vivo*

Oral preparations include liquid and coated-bead filled capsules, coated and uncoated tablets, various other attempts at sustained release preparations, and hydroalcoholic and nonalcoholic solutions. Rectal preparations include suppositories and solutions.

This disarray of formulations has resulted in confusion among physicians, the Federal Food and Drug Administration, and even among the companies that produce the drugs. To evaluate the relative merits of the various products, the following conclusions based on published data must be appreciated:

1. Benefit^{36,40-43} and toxicity (including nausea, diarrhea, vomiting, headache, seizures and death)^{42,44,45} from theophylline relate to serum concentration; 10 to 20 μ g/ml constitute conservative recommendations for the therapeutic range.⁴⁶
2. Theophylline dosage must be individualized to achieve serum levels in this therapeutic range because of variable rates for theophylline disposition.^{42,47}
3. Synergism for toxicity of theophylline and ephedrine has been demonstrated without sig-

nificant additive therapeutic effect.^{36,37}

4. The addition of a strong base to theophylline neither increases bioavailability nor decreases adverse effects.⁴⁸⁻⁵⁰ Since the solubility of theophylline in solution increases with increasing pH, these basic substances simply result in the ability to dissolve theophylline at higher concentrations.⁵¹ The addition of alcohol provides a similar advantage though still without an increase in the rate or completeness of absorption.⁵²
5. Dyphylline is a stable dihydroxypropyl derivative of theophylline with a more rapid rate of disposition than theophylline.⁵³ Its relative potency and toxicity are not defined.
6. Intramuscular theophylline (as the ethylenediamine preparation, aminophylline) is painful because of the high pH of the solution, and is slowly absorbed⁵⁴ because of theophylline's limited solubility at physiologic pH.
7. Rectal suppositories are poorly bioavailable.^{54,55} This appears to be a function of the formulation rather than the administered site since rectal solutions are well absorbed.^{55,56}
8. While bioavailability of oral theophylline is excellent, factors which delay disintegration, such as coated tablets or beads, delay absorption^{54,57} and can, as in the case of enteric coated tablets, result in highly erratic absorption and a marked decrease in absolute bioavailability.⁵⁴
9. While sustained release preparations could have a rational role for therapy with theophylline,⁴⁷ most products are insufficiently studied to justify their routine use.

In spite of the available data, fixed dose combinations of theophylline and ephedrine have been traditionally the most popular form of theophylline. Additionally, dosage recommendations among various products have been highly variable with no rec-

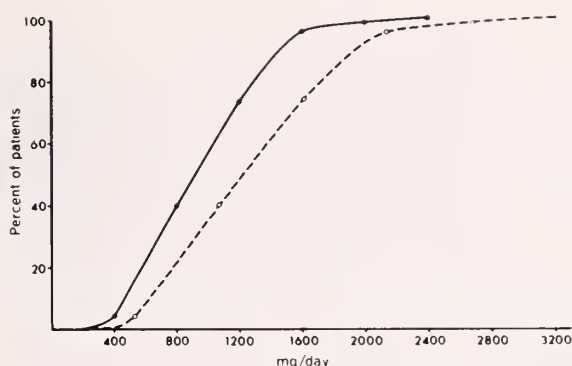
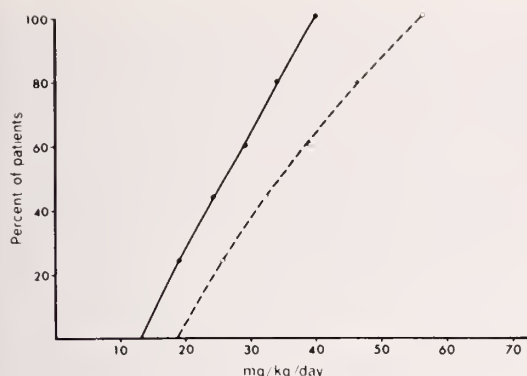


Fig. 3. Cumulative frequency distribution for theophylline dosage among children < 13 years of age (left) and adolescents-adults (right). The solid lines represent the relationship between theophylline dosage and the likelihood of exceeding 10 $\mu\text{g/ml}$ and thereby being potentially optimal for therapeutic effect. The dotted lines represent the relationship between dosage and the likelihood of serum theophylline concentrations in excess of 20 $\mu\text{g/ml}$. Thus, at the median dose (50th percentile) of 26 mg/kg/day in 4 divided doses for children and 1000 mg/day in 4 divided doses for adolescents-adults, about 25% of patients will be likely to exceed 20 $\mu\text{g/ml}$ and be at risk for toxicity.

ommendation in drug inserts regarding therapeutic serum concentrations nor even any required labeling related to actual theophylline content (Table 2). Moreover, preparations such as suppositories and enteric-coated tablets with bioavailability problems demonstrated over 25 years ago are still marketed.⁵⁴ With this disparity between practice and fact, it is not surprising that clinical impressions regarding the efficacy and toxicity of theophylline remained confused until recent studies expanded upon earlier reports and provided a data base for rational use of this drug.

Current data suggest that theophylline is potentially the most potent non-corticosteroid agent available for use in suppressing chronic asthmatic symptoms when administered in doses that achieve the therapeutic serum concentration range of 10 to 20 $\mu\text{g/ml}$.⁴⁶ This newly defined role of "prophylaxis" is in addition to its traditional function as a potent agent for acute bronchodilation during an asthmatic attack. As a result of variable disposition rates and a low therapeutic index, however, optimal benefit requires individualized chronic dosing based on serum theophylline concentration^{42,47} (Figure 3).

Theophylline clearance rates average highest in children (1.4 ml/kg/min),⁴⁷ lower in adults with uncomplicated asthma (1.2 ml/kg/min),^{42,43} and lowest in older adults with chronic obstructive pulmonary disease (0.6 ml/kg/min).⁵⁸ The longer clearances are a function of the half-life of degradation which averages 3½ hours in children⁵⁹ but may exceed 24 hours in adults with chronic obstructive pulmonary disease and cor pulmonale or other causes of heart failure⁶⁰⁻⁶² and liver pathology.^{42,63} Since benefit from theophylline relates directly to serum concentration without carryover effect,⁶⁴ rapid elimination rates, if accompanied by rapid absorption, suggest the need for unrealistically short dosing intervals. Even with 6 hourly treatment, average peak-through differences commonly exceed the 10

$\mu\text{g/ml}$ interval size of the therapeutic range.⁴⁷ Thus, a sustained release preparation, if sufficiently reliable in its absorption characteristics, would increase the practicality of maintaining serum concentrations within the therapeutic range during chronic therapy.

Since serious toxicity is not consistently preceded by minor adverse effects,⁴⁵ the adjustment of theophylline dosage must be performed cautiously. The problem is enhanced by the tendency for drug clearance to decrease as the upper end of the therapeutic range is approached resulting in changes in serum concentration disproportionate to dosage. Once a dose is established, however, the rate of disposition remains sufficiently constant over extended periods to allow continuous dosing for at least 6 to 12 months without need to routinely repeat serum theophylline levels.⁴⁷ The administration of other drugs commonly used in the treatment of asthma (e.g., corticosteroids, sympathomimetics) appears not to affect theophylline disposition. The possibility of other drugs or altered physiologic states such as fever, hepatitis, or heart failure, affecting drug metabolism must, however, be considered in patients receiving chronic theophylline and requires further investigation.

While chronic dosing relates to the variable clearance rates, initial loading doses for acute therapy relate to the more constant volume of distribution which approximates 0.5 L/kg.^{42,59} Thus, each mg/kg of loading dose will increase the serum concentration by about 2 $\mu\text{g/ml}$ (serum concentration increase = dose ÷ volume of distribution). Extremely rapid administration will, of course, temporarily overshoot this calculation because of the finite time required for distribution while excessively slow administration will allow time for significant elimination before the dose is completely administered. Administration of intravenous theophylline over 30 minutes or the use of rapidly absorbed oral preparations or rectal solutions generally results in a serum

concentration near that predicted.

Cromolyn Sodium

Cromolyn sodium is a relatively insoluble powder that requires administration by inhalation. It differs from the sympathomimetics and theophylline in that it has no bronchodilator effect at all and thus is contraindicated for acute therapy. *It is only effective as a prophylactic agent.* *In vitro* studies have demonstrated its effect as a potent inhibitor of the Gell and Coombs Type I allergic reaction⁶⁵ by blocking the antigen-induced release of histamine and SRS-A from mast cells.⁶⁶ *In vivo* confirmation of this has been obtained by demonstrating that cromolyn decreases sensitivity to inhaled antigen.^{7,67,68}

It appears, however, that not all of the clinical response can be explained by this unique mechanism since benefit is also documented for non-allergic asthma.⁶⁹ Furthermore, cromolyn has been demonstrated to decrease exercise-induced bronchospasm.⁷⁰ The mechanism of this latter cromolyn effect is not known.

Sufficient controlled studies have been performed to state unequivocally that cromolyn has a degree of efficacy in the management of chronic asthma and rarely produces serious toxicity.^{71,72} (Minor throat irritation occurs and hypersensitivity reactions have been reported.)¹¹⁶ Few studies, however, have quantitated the degree of benefit in clinically meaningful terms and it has thus been somewhat difficult to place this drug into therapeutic perspective. It was introduced into the United States market with the suggested restriction that it be limited to use in severely ill patients requiring corticosteroids; in other countries it has been used as a primary agent. Examination of the clinical data indicates that this is a weakly efficacious agent of clinical value primarily in the milder patient with chronic asthma.⁷³ For patients requiring chronic corticosteroids, benefit is less frequent and the ability to reduce or eliminate the need for corticosteroids is limited.⁷⁴

Recent reports have emphasized cromolyn's effect on exercise-induced bronchospasm.^{70,75,76} Again, examination of the data aids perspective. The suppression of exercise-induced bronchospasm is usually only partial compared with the more reliable and complete block that can be demonstrated with an inhaled sympathomimetic⁷⁶ or theophylline in therapeutic serum concentrations.⁷⁷

Thus, cromolyn is not a drug of choice for exercise-induced bronchospasm. It is least likely to be of benefit in the patient with severe disease. It is of no value in the treatment of acute symptoms. It primarily provides a potential alternative to theophylline for prophylaxis and may occasionally prevent the need for corticosteroids when added to theophylline. Its current high cost, relative inconvenience, and problems in teaching proper compliance to small children should be weighed against its high degree of safety and the avoidance of the initial

dose titration and blood level determinations required for optimal benefit from theophylline. A treatment failure rate of at least 30% is to be expected in children;⁷³ in adults an even higher failure rate has been reported.^{78,79} Since there is no way to select patients likely to respond to cromolyn, a one month trial is recommended and the drug should be continued beyond that time *only* if there is impressive control of the disease.

Corticosteroids

The glucocorticosteroids are the most effective drugs available for the treatment of asthma, but they also present a great potential for serious toxicity after chronic administration. Adverse effects include the typical Cushingoid appearance, growth suppression, muscle wasting, bone demineralization, posterior subcapsular cataracts, and other less common effects, all of which have been reviewed in detail elsewhere.⁸⁰

While efficacy in controlling symptoms is unquestioned, corticosteroids do not affect the immediate response to antigen challenge either by inhalation⁸¹ or skin testing.⁸² Various data have demonstrated that corticosteroids stabilize lysozymes, prevent reaccumulation of histamine in mast cells, sensitize beta adrenergic receptors, and also exhibit non-specific anti-inflammatory activity.⁸³ The latter complex phenomenon appears most reasonable since it fits observations that corticosteroids have a high degree of efficacy in treating asthma without inhibiting bronchospasm induced by either antigen or exercise challenge.⁸⁴

No difference in degree of effectiveness has been demonstrated among the various preparations. Individual agents include the naturally occurring agents, cortisone and hydrocortisone, and many synthetic steroids with increased potency but with similar therapeutic indices.⁸⁵ Prednisone and prednisolone are generally the preferred agents for oral medication, particularly when chronic therapy is indicated. They have less sodium-retaining effect than cortisone and hydrocortisone and can be used with greatly decreased risk of toxicity on an alternate day basis, a property not shared by other synthetic corticoids such as triamcinolone and dexamethasone which have longer durations of adrenal suppression from single doses.^{86,87}

Dose response relationships for corticosteroids have been poorly defined for asthma. While some data is available relating dosage and effect to blood level,⁸⁸ it is not clear that the maintenance of a given blood level is needed. Since acute dose-related toxicity is not apparent, massive doses (e.g., greater than 1 gm hydrocortisone) have occasionally been recommended for severe asthmatic symptoms; it is not established that such large doses are more effective than conventional 200 mg doses of hydrocortisone (or an equivalent dose of a synthetic corticoid). Benefit from this class of drugs appears to be delayed with the earliest response (increase in po_2) documented at about 3 hours after administra-

tion⁸⁵ and obvious clinical responses generally being delayed until 8 to 12 hours after a dose. This is long after peak blood levels (the half-life of prednisolone, the active metabolite of prednisone, is rarely over 3 hours).⁸⁹

A new generation of corticosteroids has recently become available. These are administered by inhalation and, unlike previously available inhaled corticosteroids (such as dexamethasone),⁹⁰ have a high ratio of topical to systemic effect. Beclomethasone dipropionate, betamethasone valerate, triamcinolone acetonide, and other similar agents appear to be effective in doses that are not associated with systemic effects.⁹¹⁻⁹³

Thus, we are seeing the third phase in the development of corticosteroid usage in the management of asthma. First, they were demonstrated effective in acute asthma with the potential to reverse severe, even life-threatening morbidity.^{4,94} Second was the demonstration that toxicity could be minimized by using alternate-day therapy with prednisone or prednisolone thus allowing sufficiently safe long-term therapy to modify treatment goals toward prevention of chronic disability.^{87,95-97} Some patients, however, will not tolerate 48 hours between medication even when high doses are used. These new agents now appear to allow continuous use of corticosteroids without significant risk of systemic toxicity.

For beclomethasone, it appears that 400 μ g/day is frequently effective and presents essentially no risk of toxicity, and even 800 μ g/day presents only small risk of adrenal suppression.⁹¹ Higher doses may, however, result in systemic corticosteroid effect. The only observed complication of these inhaled agents is occasional oral moniliasis that responds to topical therapy with nystatin mouthwash. Concern has been expressed about long-term topical corticosteroid effects on the bronchial mucosa but the currently available data do not yet support the induction of pathologic changes and neither opportunistic pulmonary infections nor atrophic changes have been seen.

Thus, it appears that the new inhaled corticosteroids are important additions to the pharmacologic armamentarium for treatment of asthma, although they still do not have the potency of systemic corticosteroids in the therapy of acute exacerbations. Furthermore, their advantage over modest doses of alternate-day prednisone (e.g., 30 mg or less of prednisone every other day) either in efficacy or safety has not been demonstrated.

Other Drugs

A variety of other drugs, both old and new, have been used or thought to be worthy of investigation for the management of asthma. Anticholinergic agents have had varying degrees of enthusiasm over the years. Atropine⁹⁸ and investigational atropine-like drugs with bronchodilator activity⁹⁹ are undergoing renewed investigation. At the present time, however, there appears to be no routine indication for the use of these agents. Alpha adrenergic block-

ers have undergone limited investigation¹⁰⁰ but their frequency of adverse effects has inhibited enthusiasm for therapeutic trials. Prostaglandins also are being investigated for therapeutic bronchodilator properties.¹⁰¹ Expectorants have long been popular but are of unproven value. Iodides, because of their potential for toxicity,¹⁰² are not recommended although one report suggests some benefit among a minority of children with severe chronic asthma (though not by any measurable expectorant activity).¹⁰³

Antibiotics are frequently administered to asthmatics because the inflammatory response of asthma is often confused with pneumonia. However, there is no indication for the routine use of antibiotics. Administration to children in status asthmaticus has been demonstrated to be of no benefit,¹⁰⁴ and transtracheal catheterizations in adults experiencing acute exacerbations of chronic asthma have not demonstrated bacterial contamination of the lower respiratory tract.¹⁰⁵

Troleandomycin, a macrolide antibiotic, has been demonstrated to be effective in severe chronic asthma^{106,107} although the mechanism of action has been felt not to be due to antibacterial activity. Recently, inhibition of theophylline metabolism by troleandomycin has been demonstrated; serum theophylline concentration doubles when troleandomycin is introduced to patients receiving theophylline.¹⁰⁸ Other effects, such as inhibition of corticosteroid metabolism, may also be responsible for the antiasthmatic effect of troleandomycin.

TREATMENT OF ASTHMA

Initial Evaluation

The use of appropriate pharmacotherapy for asthma first requires establishment of the diagnosis by providing evidence for reversible obstructive airway disease (Figure 4). This is usually strongly suspected by the history but may require confirmation by serial measurement of pulmonary function and/or response to therapy. Response to therapy must be carefully monitored and decisions need to be based on the accumulating clinical data from a rational sequence of therapeutic agents.

Minimum essential clinical evaluation requires characterization of the patients' asthma into acute or chronic disease. Since these categories are not mutually exclusive, acute therapy need not exclude planning for long-term management including identification of environmental allergens. Treatment of acute symptoms, however, has the highest priority, and until the asthma is initially controlled, etiologic factors are generally not immediately relevant to therapy. Still, pharmacotherapy should not permanently be a substitute for easily removable potent allergens contributing to chronic asthmatic symptoms.

Therapy for Acute Symptoms

An inhaled sympathomimetic agent provides the most rapid and effective means for relieving occa-

OUTLINE OF ASTHMA MANAGEMENT

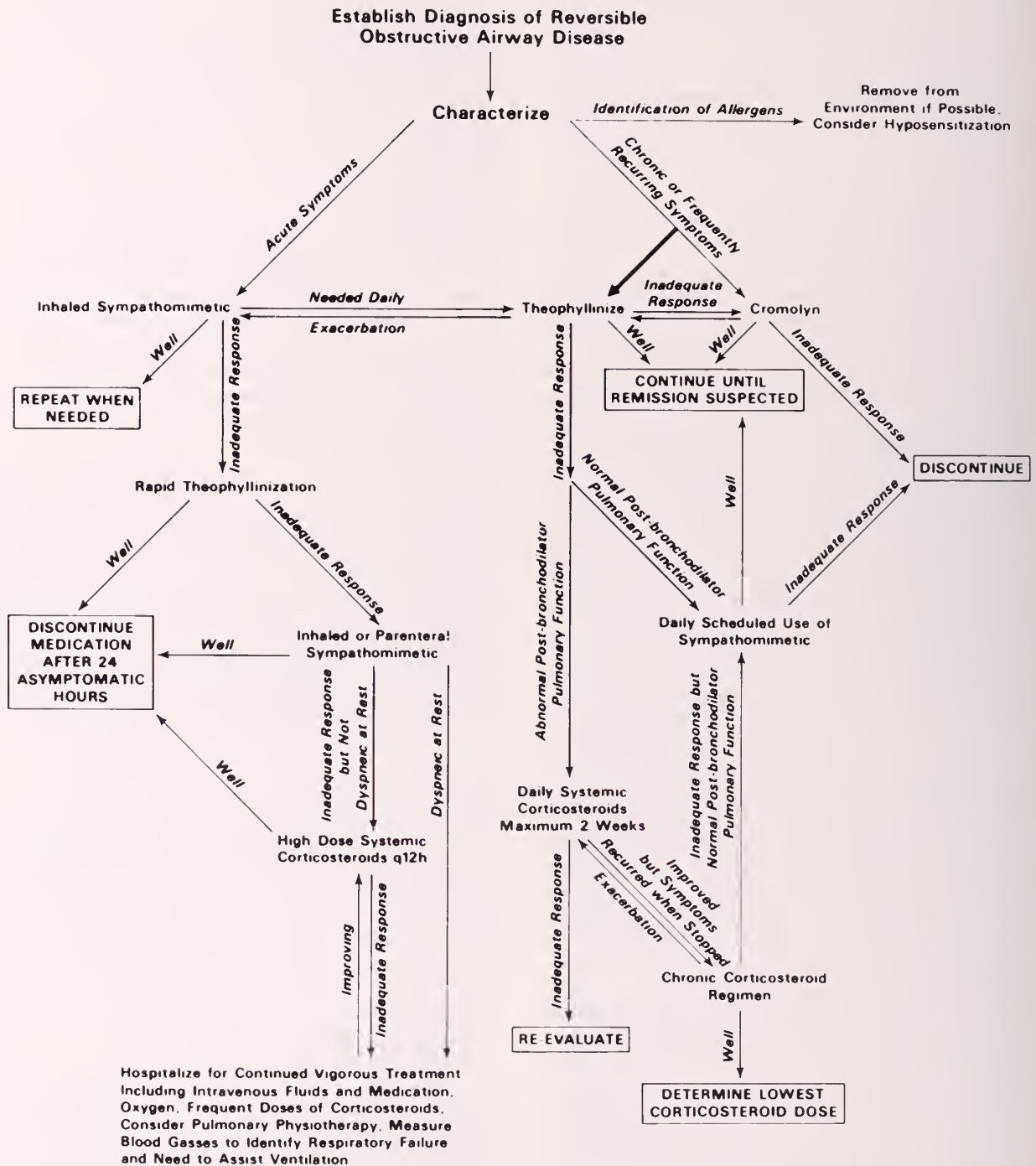


Fig. 4. Outline of asthma management.

sional acute symptoms. If these are needed on a daily basis, however, then chronic prophylactic therapy is indicated (Figure 4). Inadequate or transient relief of symptoms justifies rapid theophyllinization. If the patient has not received theophylline for the previous 24 hours, a 5 to 7 mg/kg (lean body weight) loading dose will, on the average, achieve blood levels in the range of 10 to 15 $\mu\text{g/ml}$.⁴³ A conservative short-term maintenance dose is 5 mg/kg

up to a maximum of 200 mg repeated every 6 hours. The availability of a rapid theophylline assay¹⁰⁹ is of value in monitoring acute therapy since even these conservative doses will be excessive for some and others will need more for optimal effect.⁵⁸

The route of theophylline administration under these circumstances depends on the severity of the symptoms. Oral therapy is generally an adequate route although in the small child who has been vom-

iting or who is unlikely to be cooperative with oral medication, a rectal solution provides an alternative. *Suppositories, however, have bioavailability problems and should not be used.* For more severe symptoms, the intravenous route may be indicated.

When acute symptoms continue, the repeat use of a potent sympathomimetic either by the inhaled or parenteral (e.g., epinephrine 1:1000) route may then have improved effectiveness following the loading dose of theophylline due to potential additive effects of the two drugs. If signs and symptoms are not promptly relieved by these measures, the introduction of high doses of systemic corticosteroids must be considered and, if the patient is dyspneic at rest, hospitalization is essential. The dose of prednisone, prednisolone, or parenteral methylprednisolone should be at least 1 mg/kg (rounded to the next highest 10 mg dose) up to 40 mg administered every 12 hours. Doses up to twice that administered initially and as often as every 4 hours may be needed for more severe symptoms in the hospitalized patient. Once dyspnea is relieved, administration of corticosteroids should be continued every 12 hours until the patient is completely well and has normal or near normal pulmonary functions. Tapering of corticosteroid dosage is not indicated following short-term corticosteroid usage (less than a month) since normal adrenal function returns promptly even after prolonged daily therapy.¹¹⁰⁻¹¹² The traditional tapering only serves to prolong adrenal suppressive doses and thus increase the risk of toxicity. If withdrawal of the corticosteroids results in prompt return of symptoms, then the patient may need to be treated as a chronic asthmatic (Figure 4).

Oxygen, hydration, and correction of metabolic acidosis if present are important supportive measures in the acutely ill hospitalized asthmatic. Antibiotics, expectorants, IPPB and mist are traditional but have no routine indication. Sedatives and narcotics are contraindicated. Intravenous administration of isoproterenol has been proposed as a means to treat respiratory failure¹¹³ but requires experienced personnel and cardiac monitoring equipment. In the absence of controlled studies demonstrating the advantage of this route of administration over vigorous bronchodilator therapy by more conventional routes, intravenous isoproterenol therapy should remain only in the hands of those equipped to use it. In any case, respiratory assistance may be needed when all pharmacological measures fail.¹¹⁴

Chronic Asthma

The distinction between acute and chronic asthma is not precise. Judicious use of the therapeutic measures described above can constitute good chronic management. Some patients, for example, predictably have asthmatic symptoms upon exposure to a specific allergen (e.g., a cat) or upon specific types of stress (e.g., exercise) and prompt use of a rapid-acting potent bronchodilator such as an inhaled sympathomimetic results in a period of remission until the next insult. In fact, prophylactic use of

a bronchodilator prior to the insult may be particularly useful for the patient interested in competitive athletics or even the more sedentary individual who occasionally tries hiking or jogging but finds such unusually vigorous activities poorly tolerated because of exercise-induced bronchospasm. Viral respiratory infections commonly trigger more prolonged asthmatic symptoms with a major inflammatory component of the airway obstruction. This is more resistant to treatment solely with bronchodilators and warrants the institution of a short course of corticosteroids promptly upon determination of incomplete responsiveness to theophylline and sympathomimetic bronchodilator therapy. Such treatment may prevent emergency physician visits and hospitalization, decrease the duration of morbidity, and return these patients more quickly to their usual asymptomatic state.

Many patients with asthma, however, have sufficiently frequent symptoms to make such "p.r.n." therapy inadequate. Acute treatment in such patients may induce only brief remissions and the patients' course follows a "yo-yo" pattern incompatible with a normal life. Others have continuous chronic symptoms and attempts at "p.r.n." therapy for exacerbations only treat the "tip of the iceberg." For these latter two categories of patients, continuous therapy to prevent symptoms and maintain patent airways becomes the goal.

Theophyllinization is the treatment of first choice for the management of chronic asthma. When administered continuously in doses that maintain serum concentrations in the 10 to 20 $\mu\text{g/ml}$ range, theophylline effectively decreases the frequency and severity of asthmatic symptoms, maintains its efficacy during chronic therapy, and appears safe for prolonged administration.^{36,42,46,47}

Initial theophylline doses of 4 mg/kg/dose or 100 mg/dose (whichever is the lower) administered approximately every 6 hours appear unlikely to be associated with toxicity (Figure 3). The median dose of 7 mg/kg or 250 mg (whichever is lower) can be approached from the initial dose by increments at 3 to 4 day intervals so long as adverse effects such as nausea, vomiting, diarrhea, or headache, are not observed. Because of the rising risk of exceeding 20 $\mu\text{g/ml}$ and causing toxicity as the median dose is approached, serum theophylline concentrations become indicated. A two hour sample after three days of continuous administration provides a reasonable estimate of the peak level for most products. Sustained release preparations probably produce peak levels after about 4 hours. An estimate of the trough level can be made from a pre-dose blood sample and may be of further use in adjusting dose and dosing interval. Since serious toxicity such as seizures and death can occur from excessive serum concentrations (generally $> 40 \mu\text{g/ml}$) without earlier signs of lesser toxicity, clinical titration without measurement of serum levels is discouraged.

Cromolyn may, in selected instances, be an

alternative medication to theophylline for managing chronic asthma. Its lesser potency^{77,115} and greater expense may be outweighed in some instances by its fixed dosage (20 mg by inhalation four times daily) and almost complete lack of toxicity. The addition of cromolyn to theophylline has only recently been investigated. There appears to be no contraindication to such combined therapy and it may occasionally result in additive effect.^{74,115}

Unfortunately, some patients will not respond adequately to the above measures and the use of corticosteroids must be considered. Short courses of 40 mg/day of prednisone for five to ten days may clear the inflammatory changes of asthma sufficiently to permit effective suppressive therapy with theophylline and/or cromolyn. In other patients, however, long-term use of corticosteroids is needed as alternate-day therapy with prednisone (or prednisolone) or alternatively with four times daily administration of one of the new generation of inhaled corticosteroids (e.g., beclomethasone dipropionate).

Successful long-term therapy with either alternate-day prednisone or an inhaled steroid such as beclomethasone is possible with minimal risk if excessive doses are avoided. Cushingoid changes and growth suppression are minimal with 40 mg of prednisone taken on alternate mornings^{95,97} or with 800 μ g/day by inhalation of beclomethasone dipropionate.⁹¹ Lower doses of either are often still effective and present even less risk. Higher doses increase the possibility of adrenal suppression and steroid side effects but remain preferable to even low doses of daily oral corticosteroids.¹¹² These less toxic regimens, however, also have less efficacy than daily corticosteroids. Thus, exacerbations of asthmatic symptoms resulting from airway inflammatory changes (as may occur when asthma is exacerbated by a viral respiratory infection or prolonged exposure to an inhaled allergen) may require occasional further intervention with a high dose of daily oral or parenteral steroids.

Judicious use of a sympathomimetic bronchodilator may provide further control of chronic disease by relieving occasional acute bronchospasm not completely prevented by the continuous medication discussed above. Limits must be placed on the frequency of such treatment, however, and excessive daily use may suggest the need for additional suppressive therapy.

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Reminder to M.M.A. Members

CONTINUING MEDICAL EDUCATION ACTIVITY REPORT

The bylaws of the Maine Medical Association were amended in June of 1973 as follows: Chapter I, Section 11, — "Each member of the Maine Medical Association shall be required to report his activities in continuing medical education every year according to a format provided by the Committee on Continuing Medical Education."

Only active, dues-paying members are required to report this year.

Please fill in your activity report promptly and return to the M.M.A. office, P.O. Box 250, Brunswick, Maine 04011.

Generalized Skin Eruptions During Radiation Therapy

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ABSTRACT

A series of twenty-three patients in whom a generalized skin eruption developed either during or shortly after radiation therapy has been reviewed. Five of these patients submitted to biopsy of the skin lesion.

Similar histology was found in all of the five biopsied cases and a great deal of similarity in response of the skin eruption to therapy, particularly antibiotics, was noted.

It was concluded that the skin eruptions followed the pattern previously reported in the literature as "erythema multiforme" and that they demonstrated a very similar histology. It was also concluded that antibiotic therapy has a distinct place in the treatment of this well established syndrome.

Index Terms: Skin, eruption during radiation therapy — Skin, radiation therapy.

It has been recognized for many years that radiation therapy over a localized portal or portals can produce a generalized itching eruption. This eruption has been characterized variously as erysipelas by Holmes and Shulz, "Acne"⁷ by Swift, and by a number of authors as "erythema multiforme."^{4,3,6}

To this writer's knowledge, no biopsy reports have appeared in the literature in regard to this disease and it is the purpose of this paper to cite 23 additional cases of this skin eruption, five of which have been biopsied. Another facet of this paper will be a somewhat different approach to therapy which includes the use of antibiotics.

Table 1 gives a brief summary of the clinical situation in each of the 23 cases and a more detailed summary follows in those cases where biopsy was done.

CASE REPORTS

Case Number 1. R. D. A 39-year-old white female entering with a diagnosis of squamous cell carcinoma of the cervix stage III. The patient gave no history of previous allergy and did not react to previous intravenous urogram. The patient was started on cobalt teletherapy receiving approximately 4000 rads to the entire pelvis in the midplane in one month's time. The portal size was 15x15 cm. This was followed by two radium treatments approximately one month apart. A diffuse itching rash developed after the first radium treatment. An exacerbation of the rash followed the second radium treatment. No treatment was administered following the first radium treatment but a biopsy was carried out and the following description is reported: "Skin, showing perivascular edema, capillary perivascular lymphocytic

cuffing, swelling of capillary endothelium, and slight edema of the collagen of the dermis." No thrombi or fibrinoid change. Following the second development of the rash, the patient was treated with tetracycline 250 mg. q 6 h for 3 to 6 days but did not respond. This was changed to erythromycin 250 mg. q.i.d. for 5 days and this resulted in some clearing of the rash but with persistent slight itching. The rash appeared again approximately two months following the completion of all radiation therapy and this time was treated with elixir of Benadryl® 2 tsp. t.i.d. along with erythromycin 250 mg. q.i.d. for ten days. In about two weeks the rash had disappeared. Two months later the rash appeared again and was treated by a local dermatologist with Librium® with some response over the course of the next three months. The patient is still alive and well approximately five years following therapy with no recurrence of the rash and with no recurrence of her carcinoma.

Case Number 2. C.M. A 25-year-old white female entering with a diagnosis of Hodgkins disease stage IIA with involvement of the thymus. The patient denies any history of allergy and did not react adversely to lymphangiography or intravenous urography during the diagnostic workup.

She was treated with a "mantle" port over the entire chest to include the mediastinum, both sides of the neck, and the axillae using cobalt teletherapy. This was carried out over a two-month period with 4000 rads being administered generally to all areas in the treatment field. The lung was spared as much as possible. On the 14th treatment day, the patient developed a disseminated itching rash. A biopsy was carried out before the administration of any treatment and the histological description is: "Skin showing superficial edema of the dermis and slight perivascular lymphocytic infiltration. Dilatation of vascular capillaries in superficial dermis. No vasculitis or vascular thrombosis." The patient was started on Pyribenzamine® 50 mg. t.i.d. and tetracycline 250 mg. q 6 h for 5 days and the rash had completely cleared in two days. The rash did not recur during the course of her therapy. The patient did develop a recurrence of her disease in the mediastinum approximately one year following treatment and is currently being treated with chemotherapy. The rash has not occurred.

Case Number 3. J. R. A 44-year-old white female entering with a diagnosis of malignant undifferentiated neoplasm, probably epithelial, of the left neck. Cobalt teletherapy was carried out over the course of three weeks with a dose of approximately 5000 rads delivered to the left neck using 7x8 cm. portals. By the last day of treatment, the tumor mass had disappeared. Two days before the termination of treatment a disseminated itching rash developed over the entire body. A biopsy was carried out and the histologic description is reported as follows: "The lesion appears to be fairly sharply demarcated and is mainly confined to the upper dermis. There are definite focal areas of vascular necrosis, hemorrhage and perivascular inflammation. The character and distribution of the lesion suggest the possibility of a primary injury being a vascular one associated with hemorrhagic necrosis of small vessels. There is a plugging of capillary lumina by fibrin thrombi." The pathologist went on to describe the presence of superficial edema localized with swelling and fragmentation of the elastica along with perivascular inflammation and vacuolization of the stratum corneum. Micalog® cream was immediately applied after the biopsy to areas of involvement and these areas cleared very rapidly. Figure 1 demonstrates a photomicrograph of the localized skin reaction. This was described as a "Verhoeff-VanGieson elastic tissue stain showing vacuolization of desquamating keratinized cells, edema of superficial dermis, moderately diffuse lymphocytic infiltration of dermis and fragmentation of elastic tissue."

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TABLE 1

Case	Sex	Race	Age	Diagnosis	Radiation Air Dose Area Treated	Eruption Onset	Type	Symptoms	Skin Biopsy	Treatment	Duration
1	F	W	39	Carcinoma of the cervix	Cobalt teletherapy 3300 r post. pelvis 15 x 15 cm. 3600 r ant. pelvis 15 x 15 cm. Radium 6 weeks later, and 10 weeks later	After first radium treatment. Exacerbated by second radium treatment	Diffuse erythematous with papules	Itching	Yes	Tetracycline 250 mg q 6 h for 3-6 days. No response. Erythromycin 250 mg q.i.d. for 5 days, some clearing. After 2 mo., Elixir of Benadryl 2 tsp q.i.d. for 10 days. Almost gone in 2 weeks. 1 mo. later rash reappeared. Librium. 4 mo. later rash subsiding.	11 months
2	F	W	25	Hodgkin's disease	Cobalt teletherapy 4400 r rt. axilla 8 x 10 cm. 4700 r. Mantle port 20 x 20 cm. 6000 r lower ant. mediastinum 9 x 9 cm. 4400 r lt. axilla 8 x 10 cm.	2 weeks after first treatment	Diffuse erythematous with papules	Itching	Yes	Pyribenzamine [®] 50 mg t.i.d. & Tetracycline 250 mg q 6 h for 5 days. Completely cleared in 2 days.	2 days
3	F	W	44	Undifferentiated neoplasm, lt. neck	Cobalt teletherapy 3200 r lt. lat. upper neck 7 x 8 cm. 2800 r lt. ant. neck 7 x 5 cm.	2 days before last treatment	Diffuse erythematous with papules	Itching	Yes	Mycolog cream. Rash cleared.	2 days
4	F	W	52	Carcinoma of the ovary with metastases	Cobalt teletherapy 6000 r ant. lower abdomen 20 x 20 cm. 1500 r post. lower abdomen 20 x 20 cm.	12 days after first treatment	Diffuse erythematous with papules	Itching	Yes	Elixir of Benadryl 2 tsp. q.i.d. for 3-5 days. No response. Tetracycline 250 mg. q 6 h for 3 days, rash almost gone.	4 days
5	M	W	70	Carcinoma of the lung	Cobalt teletherapy 2400 r rt. upper ant. chest 12 x 12 cm. 3000 r rt. upper chest 12 x 12	8 days after	Diffuse erythematous	Itching	Yes	Tetracycline 250 mg t.i.d. for 1 week. No response. Pyribenzamine 50 mg t.i.d. Died one week later.	
6	M	W	68	Carcinoma of the lung	Cobalt teletherapy 5600 r lt. ant. chest and mediastinum 14 x 14 cm. 4800 r lt. post. chest and mediastinum 14 x 14 cm.	Indefinite	Diffuse erythematous	Itching	No	None, patient died 1½ mo. after treatment.	
7	M	W	45	Lymphoblastic lymphoma, involving cervical nodes	280 kv HVL 3.4 mm Cu. 2400 r rt. neck 10 x 10 cm. 2400 r lt. neck 10 x 10 cm.	1 week after completion of therapy	Diffuse erythematous with papules	Itching	No	Epsom salt packs and Chlor-Trimeton [®] 8 mg t.i.d. After 9 days, no result. Some spreading. Erythromycin 250 mg q 6 h. Almost cleared in 4 days.	13 days
8	F	W	49	Hodgkin's disease	Cobalt teletherapy 4800 r ant. chest 15 x 20 cm. 1200 r post. chest 15 x 20 cm.	1 month after first treatment	Diffuse erythematous with papules	Itching	No	Pyribenzamine 50 mg t.i.d. No result. Tetracycline ordered but refused. 3 mo. later hospitalized for extensive exfoliative dermatitis.	Not recorded
9	M	W	76	Carcinoma of the lung	280 kv HVL 3.4 mm Cu. 812 r lt. lat. ant. upper chest and axilla 20 x 20 cm. 2700	After third treatment	Diffuse erythematous	Itching	No	Pyribenzamine 50 mg t.i.d. and Achromycin 250 mg t.i.d. Almost cleared in 1	1 week

Case	Sex	Race	Age	Diagnosis	Radiation Air Dose Area Treated	Eruption Onset	Type	Symptoms	Skin Biopsy	Treatment	Duration
10	F	W	66	Carcinoma of the bladder	r lt. post. chest 15 x 15 cm. 2100 r lt. lat axilla 15 x 15 cm. Cobalt teletherapy 5300 r ant. pelvis 12 x 12 cm 4000 r post. pelvis 15 x 12 cm.	2 weeks after first treatment	Diffuse erythematous	Itching	No	week, some residual itching in axilla. Periactin,* somewhat subsided after 10 days. After 16 days, Tetracycline 250 mg q 6 h for 3-6 days. Good result. Recurrence in 1 mo. after sun exposure.	Not recorded
11	M	W	57	Carcinoma of the lung	Cobalt teletherapy 2000 r rt. upper lat. chest 10 x 14 cm 2800 r rt. upper ant. chest 17 x 17 cm. 2800 r rt. upper post. chest 17 x 17 cm 2000 r lt. upper lat. chest 10 x 14 cm	1 week after last treatment	Diffuse erythematous with papules	Itching	No	Had Tetracycline before therapy. Given Chlor-Trimeton for rash, then Staphicillin for massive pulmonary infection. Died 2 mo. after completion of therapy.	Not recorded
12	F	W	37	Sclerosing Hodgkin's granuloma of paraspinal lymph nodes	280 kv HVL 3.4 mm Cu. 2100 r lt. ant. kidney area 15 x 15 cm 2100 r lt. post. kidney area 15 x 15 cm	on day of last treatment	Diffuse erythematous with papules	Itching	No	Pyribenzamine 50 mg. t.i.d. Rash gone in 11 days.	11 days
13	F	W	44	Carcinoma of the cervix	Cobalt teletherapy 4200 r ant. pelvis 18 x 14 cm. 4000 r post. pelvis 18 x 14 cm.	11 days after first treatment	Diffuse erythematous with papules	Itching	No	Tetracycline 250 mg q 6 h for 5 days and Pyribenzamine 50 mg t.i.d. Complete clearing in 1 week.	1 week
14	F	W	43	Carcinoma of the breast with regional lymph node involvement	280 kv HVL 3.4 mm Cu. 2100 r lt. ant. supraclavicular and axilla 8 x 18 cm. 2100 r lt. post. supraclavicular and axilla 8 x 18 cm.	8 days after first treatment	Diffuse erythematous with papules	Itching	No	Pyribenzamine 50 mg. t.i.d. Rash gone in 12 days.	12 days
15	F	W	58	Lymphoma involving distal colon and ileum	Cobalt teletherapy 6400 r ant. abdomen and mediastinum. 8 x 20 cm. 4400 r rt. ant. obl. abdomen 17 x 20 cm. 4400 r lt. ant. obl. abdomen 17 x 20 cm.	1 week after first treatment	Diffuse erythematous with papules	Itching	No	Pyribenzamine 50 mg t.i.d. No response after 1 week. Tetracycline 250 mg. q 6 h for 3 days. Cleared in 1 week.	2 weeks
16	M	W	78	Carcinoma of lip	280 kv HVL 3.4 mm Cu. 4130 r lower lip 3 x 5 cm.	3 weeks after first treatment	Diffuse erythematous with papules	Itching	No	Achromycin* 250 mg t.i.d. Cleared up well.	6 weeks
17	F	W	28	Multiple myeloma	280 kv HVL 3.4 mm Cu. 2100 r rt. distal femur 10 x 10 cm.	Last treatment	Diffuse erythematous with papules	Itching	No	Subsided spontaneously	3 days
18	M	W	52	Carcinoma of the lung	Cobalt teletherapy 1600 r lt. lat. chest 11 x 16 cm. 2400 r rt. lat. chest 11 x 16 cm. 2800 r rt. post. chest 16 x 20 cm. 2800 r rt. ant. chest 20 x 17 cm.	2 weeks after first treatment	Diffuse erythematous with papules	Itching	No	Pyribenzamine 50 mg t.i.d. Cleared in 1 week.	1 week
19	M	W	58	Lymphoma retro-peritoneal	Cobalt teletherapy 2400 r rt. inguinal area 8 x 14 cm. 1500	At end of therapy	Diffuse erythematous with papules	Itching	No	Tetracycline 250 mg q 6 h. 4 days. Responded to some extent.	Not recorded

Case	Sex	Race	Age	Diagnosis	Radiation Area Treated	Air Dose Onset	Eruption Type	Symptoms	Skin Biopsy	Treatment	Duration
20	F	W	55	Cancer of the skin, consistent with post breast cancer.	r lt. mid abdomen 15 x 17 cm. 3700 r lt. upper mid abdomen 15 x 17 cm. 280 kv HVL 3.4 mm Cu. 1800 r	2 months after last treatment	Diffuse erythematous with papules	Itching	No	Achromycin 250 mg q.i.d. for 6 days. Pyribenzamine 50 mg 2-3 times daily, epsom salt soak 2-3 times daily. Almost completely cleared in 2 weeks.	2 weeks
21	F	W	?	Carcinoma of the breast with regional lymph node metastases	280 kv HVL 3.4 mm Cu. 2400 r lt. ant. supraclavicular and axilla 11 x 18 cm. 2400 r lt. post. ant. supraclavicular and axilla 11 x 18 cm.	After last treatment	Diffuse erythematous with papules	Itching	No	Steroids	Not recorded
22	M	W	62	Carcinoma of the tonsil	Cobalt teletherapy 4000 r rt. lat tonsil 8 x 9 cm. 4000 r lt. lat. tonsil 8 x 9 cm.	One day before last treatment	Diffuse erythematous with papules	Itching	No	Pyribenzamine 50 mg t.i.d. Almost completely cleared up in 6 days.	1 week
23	F	W	29	Carcinoma of the cervix	280 kv HVL 3.4 mm Cu. 2400 r lt. ant. pelvis 9 x 12 cm. 2400 r rt. ant. pelvis 9 x 12 cm. 2400 r lt. post. pelvis 9 x 12 cm. 2400 r rt. post. pelvis 9 x 12 cm. Radium 1 week later and 4 weeks later	2 weeks after second radium treatment	Diffuse erythematous with papules	Itching	No	Pyribenzamine 50 mg t.i.d. for one week. Cleared up in one week.	2 weeks

This patient is alive and well 4 and one-half years following treatment and has had no recurrence of her neoplasm.

Case Number 4. M. S. A 52-year-old white female entering with a diagnosis of papillary adenocarcinoma of the right ovary with metastases to the pelvic peritoneum. The patient denies any history of previous allergy and did not react to previous intravenous urography. She received cobalt teletherapy over the course of three weeks administered to the lower abdomen and pelvis through two 20x20 cm. portals giving a dose of approximately 4000 rads to the midplane of the pelvis. There seemed to be a relative lack of response to the treatment immediately following its termination. On the 12th day of treatment, a diffuse itching rash developed. A segment of this was biopsied and reported histologically as follows: "Slight capillary perivascularitis, edema of superficial dermis, intraluminal thrombi of distended capillaries, and fragmentation and degenerative changes in elastic tissues of the superficial dermis. The nuclei of the cells lining the capillaries are large and hyperchromatic." An added note stated that the changes in the capillaries and elastic tissue were similar to those seen in the previous case. The rash was treated with Benadryl 3 to 5 days with no response and then tetracycline 250 mg. q 6 h for 3 days with complete clearing of the rash in 5 days. This patient died two years following treatment of her disease.

Case Number 5. L. P. A 70-year-old white male entering with a diagnosis of superior sulcal cancer at the right apex with destruction of at least two ribs in this area. This patient denied any allergy. There was no history of previous intravenous urography in this patient. The patient received a total tissue dose of 5400 rads through two 12x12 cm. portals directed over the right upper

chest from an anterior and posterior direction. The treatments were carried out over a 3-week period. Approximately 8 days following the onset of treatment, and initially developing within the treatment area, a diffuse itching rash spread beyond the field 2 days later. A biopsy was carried out and reported as follows: "Sections of the skin reveal the superficial epidermis to be intact. In one of the sections, there appears to be a small artificial separation between the stratum corneum and the stratum granulosum. The basal layer of the epidermis appears to show slight edema and liquefaction necrosis. There is also edema of the superficial dermis. In the superficial dermis, there are scattered focal areas of lymphocytic infiltration with rare scattered polys and occasional histiocytes. Occasional blood vessels in the dermis are surrounded by perivascular lymphocytes. The deep dermis contains moderately dense collagenous connective tissue and it was felt to represent non-specific dermatitis. Strong similarities to the previous biopsies are recorded." The patient was given tetracycline 250 mg. t.i.d. for one week without response and was started on Pyribenzamine 50 mg. t.i.d. but the patient died a week later of his disease. Figure 2 demonstrates a photograph of the skin eruption in this patient just prior to biopsy and prior to treatment.

DISCUSSION

Symptoms of arthralgia, fever, weakness, etc., have been described by other authors⁶ but were not noted in this series. While other authors have described episodes of this phenomenon developing in



Fig. 1

patients being treated for non-malignant conditions, this writer has not observed this, possibly because very little non-malignant disease is treated with radiation in this institution.

Of the various hypotheses advanced to explain the etiology of this syndrome, it would seem reasonable to assume that the radiation produces some type of triggering mechanism which reduces the skin's resistance to infection. This would be consistent with the rather indefinite relationship of the rash in many of these patients to a demonstrated response in the neoplasm.

The report cited by Maxfield and Colmann⁶ of the experience of Holzkecht in 1903 of a similar response in patients receiving radiation in relatively low quantities for benign conditions such as facial hirsutism, psoriasis or favus would seem to favor this hypothesis. Certainly, in this series of 23 cases, no distinct relationship between the onset of the rash and prognosis can be elucidated or can be concluded. As illustrated in Figure 3 and 4, there certainly is a strong perivascular inflammatory element in this syndrome and throughout the five biopsies there seems to run a theme of perivascularitis which would be most consistent with an etiology related to some type of disseminated inflammation of the skin.

The pathologist's summary of the histological

changes is as follows: "The common histologic changes appear to be primarily in the blood vessels and connective tissue of the superficial dermis. There are varying degrees of edema of the superficial dermis. There are varying degrees of perivascular lymphocytic infiltration."

"The lesions reported appear to represent variations of a primarily vascular lesion of small blood vessels of the superficial and mid-dermis of the skin."

In the treatment of this disease, it should be noted that 15 out of 23 cases responded to antibiotics or a mixture of antibiotic and antihistamine. This writer believes that this represents a significant finding and that treatment of this discomforting syndrome should consist of an initial trial of antihistamine to be followed by a course of broad spectrum antibiotics if the antihistamine does not produce the desired response.

SUMMARY

A diffuse skin eruption associated with radiation therapy and probably best characterized by the name of erythema multiforme is a well established syndrome. This report adds 23 such cases to the literature with 5 of these cases being biopsied confirming the similarity of the lesions.

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Drug Induced Hypoglycemia and Hypothermia

W. PHELPS CARTER, JR., M.D.*

Practicing physicians are often faced with a subnormal temperature and consider diurnal variation, cold exposure or infection as possible causes. The presence of hypothermia below 96 may indicate the presence of hypoglycemia, a life-threatening condition. Physicians should be alerted to the fact that hypothermia may be a clinical sign of hypoglycemia in the conscious and unconscious patient.

CASE REPORTS

Case 1. A 52-year-old black alcoholic was brought to the Emergency Department by the rescue unit with the history of passing out for an unknown length of time. He admitted to heavy alcoholic consumption for the preceding twenty-four hours. Physical examination revealed a disheveled male with alcohol on his breath. Vital signs were, temperature 94° (rectally); pulse 100; respirations 15; and blood pressure 120/84. He was oriented to person, place and time. A disposition to one of the local alcoholic shelters was to be made except for the patient's persistent hypothermia. After two hours in the Emergency Department, the patient remained hypothermic and was found babbling incoherently. He was admitted to the hospital with the diagnosis of acute alcoholism with hypothermia secondary to exposure and alcohol abuse. A review of the patient's past admissions revealed that two years prior the patient was admitted with a core temperature of 75° which responded to warming blankets and IV fluids (Dextrose). He recovered with no specific complications.

On this admission, the laboratory reported a blood alcohol of 95 mg % (intoxicated level = 150 mg %) and a blood sugar level less than 10 mg %. Patient was given 50% Dextrose with dramatic improvement in his mental status and gradual elevation of body temperature.

Case 2. A 38-year-old known juvenile diabetic controlled on 40 units NPH U-100 was found cold, unresponsive and foaming at the mouth. He was transported to the Emergency Department arriving with generalized seizure activity. The night prior to admission moderate alcohol consumption was documented. Temperature 94.7° rectally, pulse 72, respirations 20, blood pressure 120/70. IV 50% Dextrose and 5 mg IV Valium® were administered. The patient recovered uneventfully. His temperature being 96.8° two hours after admission.

Laboratory results were blood sugar 20 mg %. No alcohol level was obtained.

DISCUSSION

Both of these cases represent examples of hypothermia indicating hypoglycemia. The drugs responsible for the hypoglycemia were alcohol and insulin. Both cases presented with hypothermia at various stages of hypoglycemia encephalopathy. Case 1 the patient was conscious but became gradually obtunded. Case 2 the patient was comatose.

Hypoglycemia encephalopathy represents a metabolic disorder where cerebral glucose is depleted often less than 20 mg %. Brain destruction

occurs as cerebral oxidation occurs without glucose. Neural lipid and protein are metabolized. Nervousness, hunger, confusion, coma and a drop in core temperature due to thermoregulatory dysfunction are seen in varying stages of hypoglycemia encephalopathy.

In the alcoholic, hypoglycemia may result from two possible mechanisms. The first may be severe hepatic parenchymal damage with decreased gluconeogenesis and glycogen reserves. The second and more common cause is direct nutritional decrease in glycogen reserves with concomitant inhibition of gluconeogenesis. Field et al¹ found that hypoglycemia in the alcoholic was induced by ethanol consumption in combination with poor dietary intake. Controls with non-alcoholic individuals who fasted for two days with ethanol ingestions produced hypoglycemia.

Classically seen in the diabetic patient, hypoglycemia with resultant hypothermia can occur in other clinical situations. Kedes and Field² related five cases of hypothermia. One case was a woman brought to the Emergency Department in a catatonic state with no available history. A psychiatric consult concurred on the diagnosis and while the patient was being transported to the psychiatric unit, a nurse reported a rectal temperature of 95° F (35°). An emergency blood sugar was obtained with blood glucose reported 14 mg %. The patient became lucid after administration of 50 cc of 50% Dextrose and a diabetic history was obtained.

A second case of a 46-year-old black woman with carcinoma of the liver who presented with weakness and rectal temperature of 95.9° F (35.5°). Initially felt due to progression of her hepatic carcinoma, the hypothermia was ignored. A blood sugar was finally obtained. The result was 28 mg %. Both of these cases further demonstrate the diagnostic trap that physicians experience in dealing with hypothermia as a sign of hypoglycemia.

The actual physiologic mechanism of hypothermia in the presence of hypoglycemia remains unclear. Freinkel et al³ used 2-deoxy-D glucose (2-DG) to induce hypothermia in mice. 2-DG specifically inhibits intracellular utilization of glucose. These investigators found that hypothermia was related to neural intracellular glucose levels and not to the availability of circulating glucose. Specific hypothalamic centers with glucose sensitivity have been suggested.⁴ Recent studies also suggest insulin sensitive hypothalamic centers.

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THERE ARE A LOT OF PEOPLE GETTING BETWEEN YOU AND YOUR PATIENT.

Medicine today is in the spotlight, subjected to all kinds of scrutiny. Your control over patient therapy is being monitored, judged and occasionally abrogated, sometimes by unknown third parties.

The worry is that in the wake of this focus, the relationship between you and your patient will be weakened, without offsetting benefits. Consider three examples:

Drug substitution In most states, pharmacy laws, regulations or professional custom stipulate that your non-generic prescriptions be filled with the precise products you prescribe. But in the last five years, a dozen or more State laws have been changed, permitting the pharmacist in most cases to select a product of the same generic drug to fill any prescription.

Ironically, this dilution of physician control has taken place against a background of growing evidence that purportedly equivalent drug products may be inequivalent, since neither present drug standards nor their enforcement are optimal. In fact, the FDA itself says it has not enforced the same standards for hundreds of "follow-on" products that it had applied to the original NDA approvals. Thus physician control over patient therapy is being eroded with a risk that patients may be exposed to drugs of uncertain quality.

The major advertised claim for substitution is reduced prescription prices for consumers. Yet no documentation of any significant savings has been produced.

MAC Maximum Allowable Cost, MAC for short, is a Federal regulation designed to cut the Government's drug bill by setting price ceilings for drugs dispensed to Medicare and Medicaid patients. Unless the prescriber certifies on the prescription that a particular product is medically necessary, the Government intends to pay only for the cost of the lowest-priced, purportedly-equivalent,

generally-available product. The effect of the program may be that elderly and indigent patients will be restricted to products which someone in Washington believes are priced right. Practicing doctors will have little to say about administration of the program, since Government will have absolute authority to make its choices stick.

The drug lag The future of drug and device research depends upon a scientific and regulatory environment that encourages therapeutic innovations. The American pharmaceutical industry annually is spending more than \$1 billion of its own funds and evaluating more than 1,200 investigational compounds in clinical research. Disease targets include cancer, atherosclerosis, viruses and central nervous system disorders, among others. But there is a major barrier to the flow of new drugs to your patients: The cost of the research is more than ten times what it was, per product, in 1962; and whereas governmental clearance of new drug applications took six months then, it commonly consumes two years now.

The FDA needs adequate time, of course, to consider data. But it is equally clear that the present approval process contributes to needless delay of needed therapy. That's why the increased efficiency of the drug approval process is vital to all our futures.

If these issues concern you, we suggest that you make your voice heard—among your colleagues and your representatives in State legislatures and in Washington.

It could make a difference in your practice tomorrow.



Pharmaceutical Manufacturers Association
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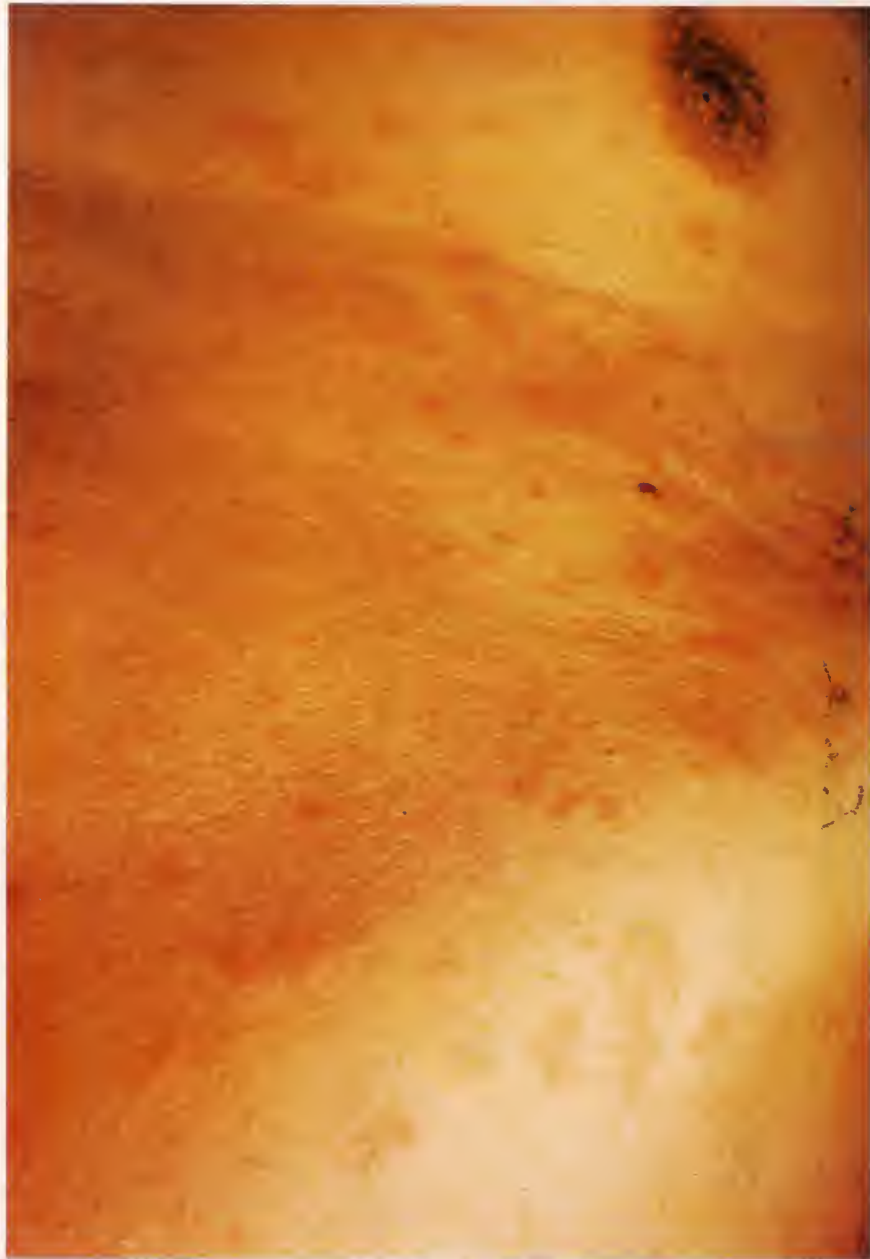


Fig. 2

This report also suggests the advisability of broad spectrum antibiotics over a period of 3 to 5 days in the treatment of this syndrome.

ACKNOWLEDGEMENT

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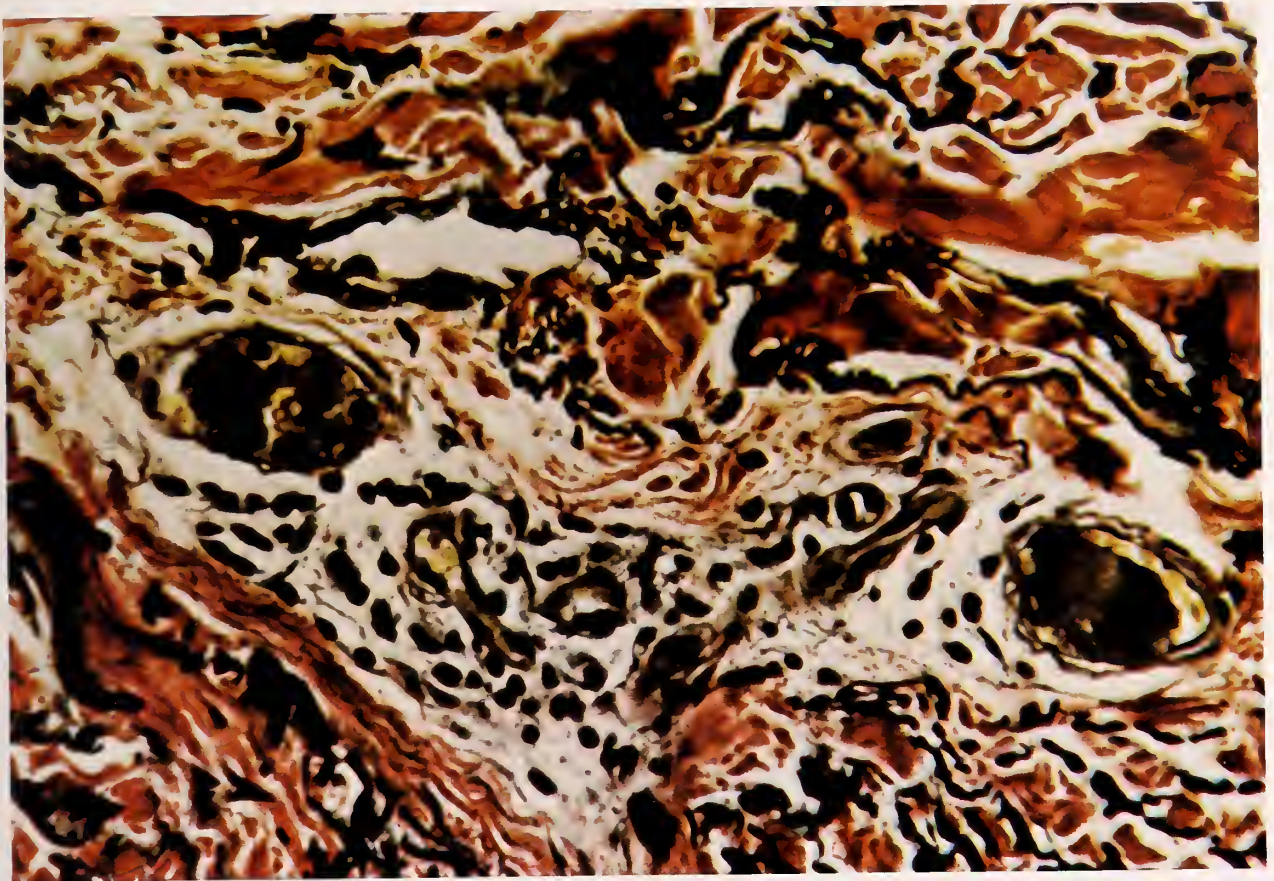


Fig. 3

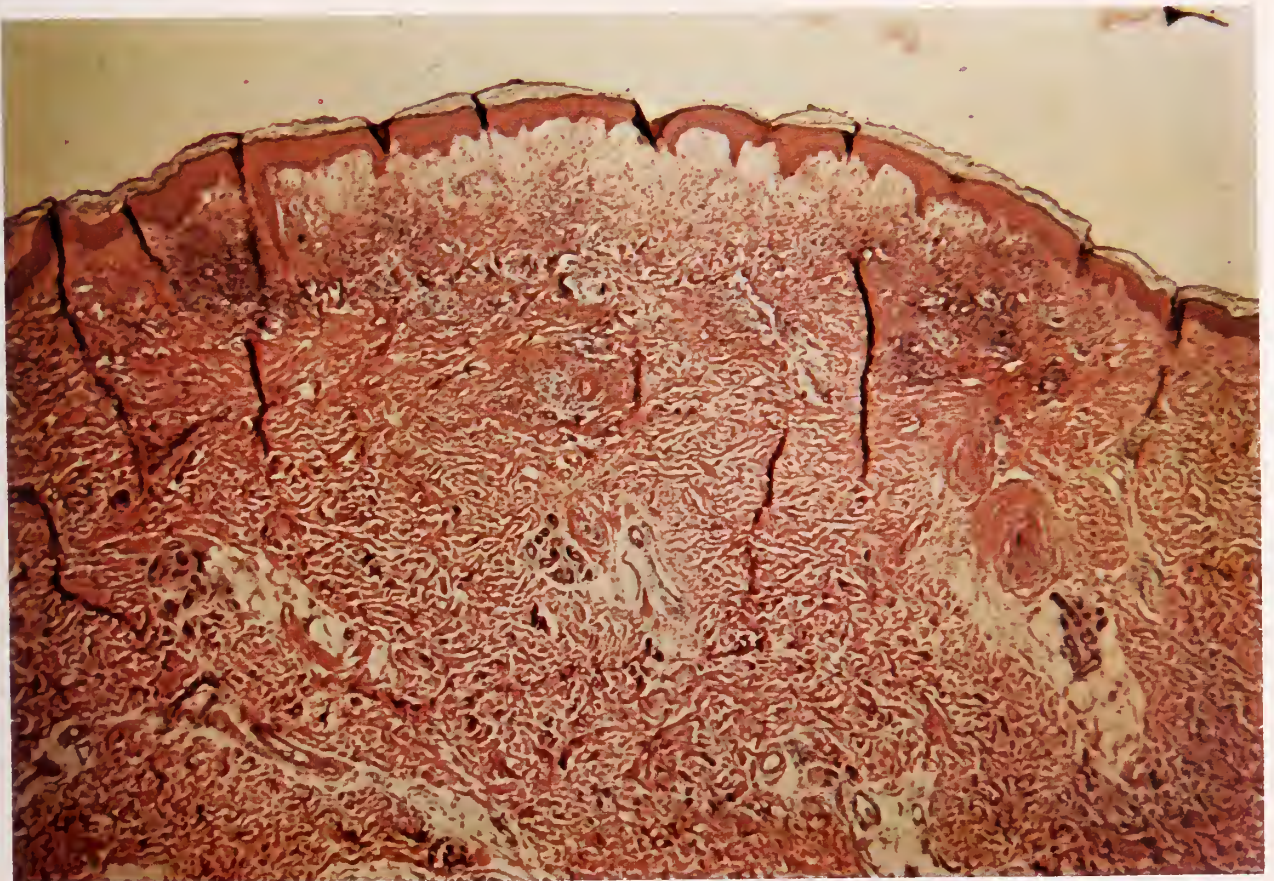


Fig. 4

How to Influence Physicians Decisions for Rural Practice

MARK KAUFMAN*

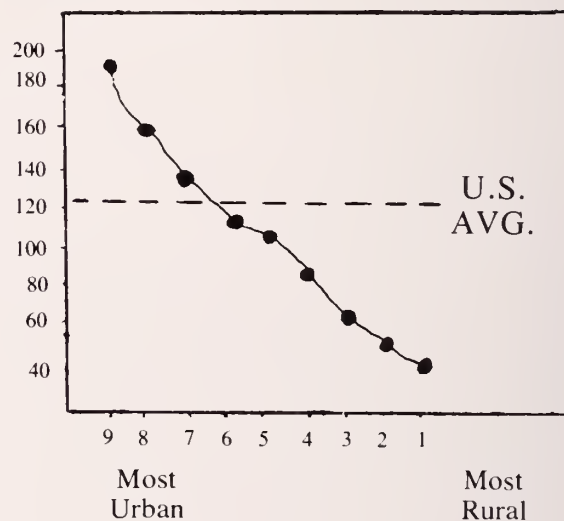
ABSTRACT

The purpose of this paper is to systematically organize and evaluate the factors affecting the decision for rural practice in the hope of subsequently realizing the most practical and effective means of positively influencing that decision. The decision for rural practice is reviewed within a framework of five levels of influence: the medical school admissions process, the medical school period with emphasis on rural preceptorships, the postgraduate training period, the professional environment of the community of medical practice, and the non-professional aspects of that community.

INTRODUCTION

Attempting to increase the number of rural physicians via the medical school admissions process seems most impractical. Similarly, the non-professional aspects of the community of medical practice offer little opportunity for active intervention and influence on the decision for rural practice. Medical student rural preceptorships hold great potential as a vehicle for attracting prospective physicians to rural areas, but the preceptorship must expose the student to a rural practice without the work overload and professional isolation often found in rural practice. Post-graduate training in rural areas under the supervision of small community oriented physicians seems a practical, effective, and probably critical means of attracting young physicians to rural environments. Just as critically, the professional working environment exerts enormous influence on the decision for rural practice, and ready access to membership in a group practice represents the essential positive component of the environment. Documentation of the inadequacy of rural health care delivery in this country is both abundant and convincing.¹ Perhaps the most dramatic indication of the anemic state of rural health care is reflected in the enormous discrepancy between the number of physicians practicing in urban versus rural environments (Figure 1).² Furthermore, researchers predict an ever greater shortage of rural physicians in the future.¹ The need for attracting more physicians to rural areas is as obvious as are the consequences of failing to meet that need.

In response, some researchers have explored the multitude of factors which attract physicians to or discourage them from rural practice. Others have, more specifically, investigated the influences which



County Classification
(Figure 1)

Nonfederal physicians in the United States in direct patient care per 100,000 population, 1970.²

the rural preceptorship at the medical student level and the period of postgraduate training exert on later practice location. Still others have opted to focus upon the medical school admissions process as the means by which to increase the number of rural physicians. However, from the information that these many worthwhile though separate endeavors provide, there has yet to emerge a synthesis of information and a comprehensive analysis dealing with the decision for rural practice and the most effective ways of influencing it.

The goal of this paper is to organize and evaluate the information these studies provide relating to that decision, and thereby to realize the most practical and efficient means of relieving the shortage of physicians in this country's rural areas. I propose to analyze the decision for rural practice by organizing the multitude of factors contributing to or affecting that decision into five levels of influence which, theoretically, represent the principle potential vehicles for effecting a change in attitudes towards rural practice and, therefore, the number of rural physicians. These five levels of influence are as follows: (1) the medical school admissions process, (2) the medical school period, specifically the rural preceptorship, (3) the postgraduate training period, (4) the professional environment in the community

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of medical practice, and (5) the non-professional characteristics of the community of practice.

MEDICAL SCHOOL ADMISSIONS

The first level of influence which some researchers have investigated as a potential means of increasing the number of physicians interested in rural practice is the medical school admissions process. The opportunity to select out from the college applicant pool prospective medical students with specific desired characteristics certainly exists when, for example, in 1974-1975 there were greater than 42,000 applicants to U.S. medical schools for less than 15,000 first year places.³ But are there indeed specific characteristics which will validly predict later practice location?

The most significant correlation is that physicians who grew up in small or rural communities are most likely to locate their practices in such communities compared to urban reared physicians.¹ Additionally, a physician's wife, when also reared in a rural environment, exerts an independently direct and positive influence on the physician-husband's decision to locate in a rural environment.⁴ The influence of the spouses background is not as significant upon those doctors planning urban practices.⁴ One study concludes that "when both the physician and his wife are from a rural background, they should be considered as having the highest likelihood of selecting a rural location."⁵ Furthermore, a direct relationship apparently exists between interest in family practice and plans for rural practice.⁴

Clearly, then, medical schools committed to increasing the number of physicians practicing in rural areas should optimally admit married students professing interest in family practice who themselves grew up in a rural environment as preferably did their spouses. The problems are obvious.

First of all, a professed interest in family practice does not mean eventual entrance into that field; likewise, plans for rural practice do not necessarily translate into actual practice years later. Secondly, how many medical school applicants are indeed rural reared, how many are married at that time, and what percentage of those students married also have rural reared wives? These are very important questions to answer if one wishes to influence at the medical school admissions level the number of physicians migrating to rural areas.

Additionally, one survey reveals that only 14.2 percent of primary care physicians were certain before entering medical school of their eventual practice location.⁵

Finally, how quickly will medical school admissions committees alter their focus from MCAT scores, GPAs, etc. to applicant backgrounds and applicant spouse backgrounds? One study reveals no discrimination against rural applicants but a proportionately low number of rural reared applicants to medical schools.¹⁰ Indeed, just how deeply are admissions committees committed to improving

rural health care delivery? The problems inherent in increasing the number of rural physicians at medical school admissions level are both multiple and difficult.

MEDICAL STUDENT PRECEPTORSHIPS

The second level of influence proposed is the medical school experience itself, particularly the effect of rural preceptorships. In the past, the medical school period has not generally represented enough time to have a significant effect on the decision for rural practice in that only 10.6 percent of primary care physicians seem to decide for rural practice during their medical school tenure.⁵ However, the hope exists that a medical student experience in rural health care delivery, usually via preceptorship, might positively influence future attitudes towards rural practice.

A major study attempts to analyze the relationship between medical student participation in rural training programs, including preceptorship, and the decision to locate medical practice in rural areas.⁶ This study concludes that, overall, the impact of such programs on future practice location is relatively slight. Many of the students are apparently inclined towards rural practice before participation. Indeed, the greatest impact of such programs is upon urban reared physicians in non-primary care specialties, presumably by exposing them to previously unfamiliar life and medical practice styles.⁶

The study also links the reluctance of physicians to establish their practices in rural areas to the fear of professional isolation.⁶ These findings suggest that the potential of preceptorships to attract physicians into rural areas would be significantly enhanced if the preceptorships are more oriented toward urban reared students, and if, more importantly, the preceptorships provide experiences with physicians in rural areas who have somehow overcome professional isolation for instance, in rural group practices. Clearly, a medical student preceptorship in a rural area with a professionally isolated solo GP is more likely to negatively influence the decision for rural practice. Just as clear, however, is the potential of a rural preceptorship in the correct professional setting to influence urban oriented medical students to seriously consider rural practice.

POST DOCTORAL TRAINING

The third level of influence upon the decision for rural practice is the period of post-graduate training. Researchers have demonstrated that this time period is critical with respect to deciding practice location.⁷ One study reveals that 45.8 percent of primary care physicians select their practice location during internship, residency, or other house staff training.⁵ The two principal influences during this time period relate to the geographic location of the training institution and to house officers' colleagues and teachers.^{1,7}

One study concludes that those who train in urban places tend to locate in urban places, and that, as a result, one can potentially supplement the population of rural physicians by developing more training facilities in rural areas.¹ However, that same study cautions that urban oriented students, and that other biases might overstate the association between training location and practice location. Yet, the conclusion of the student preceptorship study previously discussed suggests that training in an optimal professional and rural setting may significantly and positively influence a house officers decision for rural practice.

The second major influence on the house officers decision for practice location is exerted by his colleagues and teachers. This influence is well documented in a study which investigates the attitudes of physicians towards rural practice.⁷ The authors demonstrate, for example, that a majority of large community physicians express a preference for large community living, feel deterred from rural practice because of a lack of clinical support from a large medical center, and regard small communities as lacking complete medical facilities. The authors conclude that these and similar attitudes of large community physician-professors would negatively influence a house officers decision for rural practice.

Furthermore, to support the significance of this mentor influence, this same study reveals that an average of approximately 80 percent of both large and small community physicians surveyed, list the influence of colleagues and professors during training as an important factor deterring physicians in general from locating in a small community. In addition, less than 20 percent of small community physicians cite the influence of colleagues and professors during training as an important positive factor influencing them personally to locate in a small community.⁷ That most physicians train under the supervision of large community oriented physicians would seem to exert a very significant negative influence on the decision for rural practice.

It is apparent from the above discussion that both the geographic location of training and the attitudes of the clinical professors exert major influence on the house officers decision for practice location during a critical time period when nearly half of all primary care physicians decide their practice location. The potential positive effect on the house officers decision for rural practice via training in rural areas with small community oriented teachers is great.

PRACTICE ORGANIZATION

The fourth and very important level of influence upon the decision for rural practice is the professional environment in which the physician practices. Great insight into the importance and nature of this influence comes from a study which focuses upon the reasons physicians leave primary care practice.⁸ At least two-thirds of those physicians

surveyed who did abandon primary care practice relate the degree of overwork as the principal reason. This encompasses the long hours of work and the physical and emotional strain of feeling unable to get away. Significantly, no one cites a lack of challenge or boredom as a cause for leaving. Additionally, the physicians also suggested measures which they believed would enhance primary care practice: association with house officers and medical students (74 percent), residency programs in primary practice (81 percent), and group practice (96 percent).⁸

As suggested above, group practice is one of the important components of viable professional environments. Three out of four established physicians, if they had to do it over again, are reported to feel that they would choose group practice over solo practice.⁹ In a ranking by primary care physicians of factors most important in their location decision, the most important single factor is the opportunity to join a desirable partnership or group practice (43 percent). Fear of professional isolation is an extremely important factor deterring physicians from rural practice.⁷ Money should not constitute an important factor in the decision for rural practice since rural physicians earn as much as non-rural physicians, although the non-rural doctors are not often cognizant of this.¹ Only 16 percent of primary care physicians apparently consider income potential as an important factor in the decision for rural practice.⁵

Clearly, ample opportunity for group practice is an important component of the rural professional environment which may attract practicing physicians. The demand is clear. Group practice can significantly reduce the work overload of primary care physicians and can nullify the fears and realities of professional isolation in rural areas, the two major objections to primary care practice. Other positive features, from the rural practitioners point of view which should optimally be incorporated into the rural professional environment include residency programs and medical student preceptorships.⁸ House officers and medical student contact with contented rural practitioners in a group setting would reciprocally have a very beneficial and influential effect on their decision for rural practice. It is increasingly obvious that the professional environment exerts tremendous influence of the decision for practice location, and the essential component of the professional environment is the ready availability of group practice.

COMMUNITY IMPACT

The fifth and final level of influence on the decision for rural practice concerns the non-professional aspect of the community in which the physician practices. In the study of physicians who leave primary practice, 58 percent complain of inadequate cultural and recreational resources.⁸ In another study in which primary care physicians rank factors

that constitute an important influence on their practice location, the second most important factor, overall, is the climate or the geographic features of the area (35 percent).⁵ Fourth most important (21.5 percent) is the individual physicians preference for rural or urban living. Other ranked though less prominent factors include recreational sports facilities (12 percent), quality of the educational system for children (10 percent), and cultural advantages (8 percent).⁵

Thus, non-professional community characteristics do indeed influence a physicians relative attraction to a community, large or small, urban or rural. The most important factors do not seem to favor urban over rural communities. Moreover, different rural communities may contrast greatly with respect to their non-professional features. Therefore, although one cannot deny the influence of the non-professional aspects of a community upon the decision to locate practice, the important components exerting the influence can neither be generalized to all rural communities or into an urban versus rural dichotomy. Additionally, little potential exists for manipulating these specific community characteristics in order to positively affect the decision for rural practice.

CONCLUSION

Attempting to increase the number of rural physicians via the medical school admissions process seems most impractical. Similarly, the non-professional aspects of the community of medical practice offer little opportunity for active intervention and influence on the decision for rural practice. Medical student rural preceptorships hold great potential as a vehicle for attracting prospective physi-

cians to rural areas, but the preceptorship must expose the student to a rural practice without the work overload and professional isolation often found in rural practice. Post-graduate training in rural areas under the supervision of small community oriented physicians seems a practical, effective, and probably critical means of attracting your physicians to rural environments. Just as critically, the professional working environment exerts enormous influence on the decision for rural practice, and ready access to membership in a group practice represents the essential positive component of the environment.

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DRUG INDUCED HYPOGLYCEMIA AND HYPOTHERMIA — Continued from Page 272

Other drugs besides alcohol and insulin may produce hypoglycemia with hypothermia. Salicylate and sulfonylureas ingestion may produce hypoglycemia. In the overdose patient, the presence of hypothermia may indicate possible hypoglycemia. Below are listed major drugs producing hypoglycemia; not all produce hypothermia.

Individual Drugs*

Alcohol
Insulin
Salicylates
Sulfonylureas
Para-aminobenzoic Acid — rare
Propoxyphene hydrochloride (Darvon®) — rare

*Reprint — *Hospital Physician*®, May 1975, F. & F. Publications, 1975.

Drug Combinations

Insulin plus sulfonylureas, alcohol, propranolol hydrochloride (Inderal®), oxytetracycline (Terramycin®), or disodium edetate (Endrate, Sodium Versenate).

Sulfonylureas plus alcohol, salicylates, phenformin hydrochloride (DBI®, Meltrol®), sulfisoxazole (Gantrisin®), dicumarol, or phenylbutazone (Azolid®, Butazolidin®).

SUMMARY

Hypothermia in some clinical settings may indicate hypoglycemia. Hypothermia may occur with minimal signs of hypoglycemia encephalopathy. Physicians should be reminded that the standard oral thermometers do not go below the starting point when recording temperatures. Other drugs besides alcohol and insulin may produce hypothermia in the conscious and unconscious patient. Hypothermia remains a valuable clinical sign of possible hypoglycemia.

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Hypertension Control in Rural Maine

Franklin County High Blood Pressure Program

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INTRODUCTION

High blood pressure (HBP) is a public health problem of major proportions. Although common, dangerous, and treatable, HBP frequently goes undetected; when detected is often not treated; and when treated is often inadequately controlled.

Impeding satisfactory control are various medical, professional, educational, and socio-economic obstacles. Among these are the large numbers of people affected, uncertainties of diagnostic criteria and routine workup, patient non-compliance and loss to follow-up, cost and side-effects of medication, inaccessibility and cost of health care, professional and public ignorance and misconception, and failure of many health professionals and facilities routinely to screen for hypertension.^{1,2,3}

PROGRAM EVOLUTION

Across the nation, hypertension control has been the focus of community-based projects. One of these, the Franklin County High Blood Pressure Program (FCHBPP), has developed in its first year a multifaceted approach to the challenges of HBP education, detection and follow-up in rural, west-central Maine.

West-central Maine constitutes a 1900 square mile area in the foothills of the White Mountains. A population of 28,000 resides in 29 communities ranging in size from 5 to 5,600 people. Poverty is a fact of life here; 22% of families receive Aid for Dependent Children and 50% of families earned less than \$5,000 in 1970. Logging, paper, wood products, shoe making and recreation provide the major employment opportunities. Roads are good, but there is no public transportation. Inpatient medical care is provided by the Franklin County Memorial Hospital. Most of the 20 area physicians are on the medical staff of this 80-bed facility.

The Program began in April 1974 as a small-scale educational and detection project sponsored by the medical staff of the Franklin County Memorial Hospital (FCMH). Endorsement by the 1125th U.S. Army Reserve Hospital allowed the Program's director (NBR) to substitute community HBP presentations in place of regular Reserve meetings. A grant from Maine's Regional Medical Program (RMP), provided funds for salaries and operating expenses.

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TABLE 1

AGE SPECIFIC UPPER LIMITS OF NORMAL BLOOD PRESSURE		
AGE, YRS.	SYSTOLIC	DIASTOLIC
6-12	130	80
13-20	130	85
21-40	140	90
41-60	150	90
61-80	160	95
Over 80	170	100

Logistical and administrative support was provided by Rural Health Associates (RHA), a multi-specialty, comprehensive care, group practice with which the Program's director is associated.

PROGRAM DESCRIPTION

Crucial to the function of the Program is a network of community blood pressure centers which provide free blood pressure checks on a regular weekly or biweekly schedule in 15 area towns. Located in banks, churches, municipal buildings and other convenient locations, these centers have been staffed by over 200 volunteer nurses and clerical personnel. Many patients come to the center of their own volition; others are referred by physicians.

To function adequately, this network requires considerable central coordination and administration. Forms must be devised, compiled and distributed. Accuracy of classifications must be verified. Equipment must be distributed and maintained. Newspaper and radio advertising must be written and coordinated. Records must be kept. Follow-up must be pursued. These functions and more are performed by the program coordinator (medical assistant) working 30 hours/week, under the supervision of a physician program director working 6 hours/week.

Using age-specific criteria approved by the hospital medical staff (Table 1), each patient is told his own BP, whether normal or elevated, and an action plan is recommended. If either systolic or diastolic pressure is elevated, the patient is advised to return to the center for recheck. Three consecutive elevated pressures call for referral to the personal physician for evaluation and possible therapy. If pressure returns to normal on second or third visits, labile HBP is presumed and the patient advised to have his BP checked at least every 6 months. Patients with treated HBP are encouraged to continue treatment if their BP is within normal limits, or to contact their physician if elevated.

High blood pressure screening has been implemented in many other settings. Most major in-

dustries have assisted in screening their employees. Special screenings have occurred at the County Fair, a hospital open house, and some of the area's largest shopping centers. Numerous civic, religious, and social groups have participated in educational and screening sessions. Some dentists, optometrists, and druggists have made BP checks part of their routine. BP measurement is now standard procedure in the hospital emergency room.

Educational efforts have kept pace. A weekly 5-minute radio presentation has been supplemented by several half-hour talk shows. Local newspapers regularly carry articles about HBP and the Program. HBP and related cardiovascular diseases have been major topics in health courses at University of Maine at Farmington. Over 400 patients have viewed a teaching film on HBP. Many have received specially prepared sheets describing their own particular anti-hypertensive medication. HBP and the Program often have been a topic at hospital medical staff meetings.

RESULTS

During the first 12 months of Program operation, 12,000 BP measurements were performed on 4,680 people, or 23% of the area population over age 15.

A subgroup of the total population screened — those seen during the first 6 months of the Program in 7 of the 15 centers — was studied in detail. Between December, 1974 and June, 1975, 2532 people were checked at the 7 centers: of these, 1258 (50.3%) had either elevated BP on their first encounter, or were normal on hypertensive medication.

Of this large group with initially elevated or adequately treated blood pressure, 49% denied prior knowledge of their HBP, 11% had been told but were not on treatment, 25% were above normal despite treatment, and 14% were within normal limits on treatment. Similar proportions were found in the National Health Survey, 1960-62 (Table 2).⁴

Of 710 with mild-moderate, untreated elevations initially, 37% returned to normal without treatment (labile HBP) on follow-up visit. Persistent but as yet untreated HBP was documented in 11%. Four percent were still hypertensive despite new treatment; and 6% were adequately controlled with treatment. The largest subgroup, 42%, had not returned for the two follow-up visits required for classification as either labile or sustained HBP.

People with severe elevations initially (systolic 60 m.m. or diastolic 30 m.m. above normal limits) were advised to see their doctor directly rather than return for Program confirmation. Thus, of 61 people in this high risk category, 67% had no further Program contact and their status was unknown. Thirteen percent did return, still had HBP, but had not seen a physician; 9% were on treatment, but still above normal; and 11% had accomplished good BP control with treatment.

Of 215 patients with previously diagnosed and

TABLE 2

CATEGORY	FCHBP		NHS
HBP, Total patients	1258	100%	100%
UNAWARE of HBP	622	49%	43%
Aware, NOT TREATED	142	11%	22%
Treated, NOT CONTROLLED	312	25%	19%
Treated, WELL CONTROLLED	182	14%	16%

treated but incompletely controlled HBP initially, 38% had become well-controlled (within normal limits) by their latest visit. Among 182 with well-controlled HBP at their first visit, only 7% were known to have reverted to elevated levels.

Comparing first and latest Program contact, the number of patients taking antihypertensive treatment rose from 494 to 570, an increase of 15%. The number of patients with treated, well-controlled HBP rose from 182 to 332, an increase of 82%. Excluding those with documented labile hypertension, the proportion of hypertensive patients on treatment increased from 50% to 58% and the proportion with treated, well-controlled HBP rose from 18% to 34% (Fig. 1).

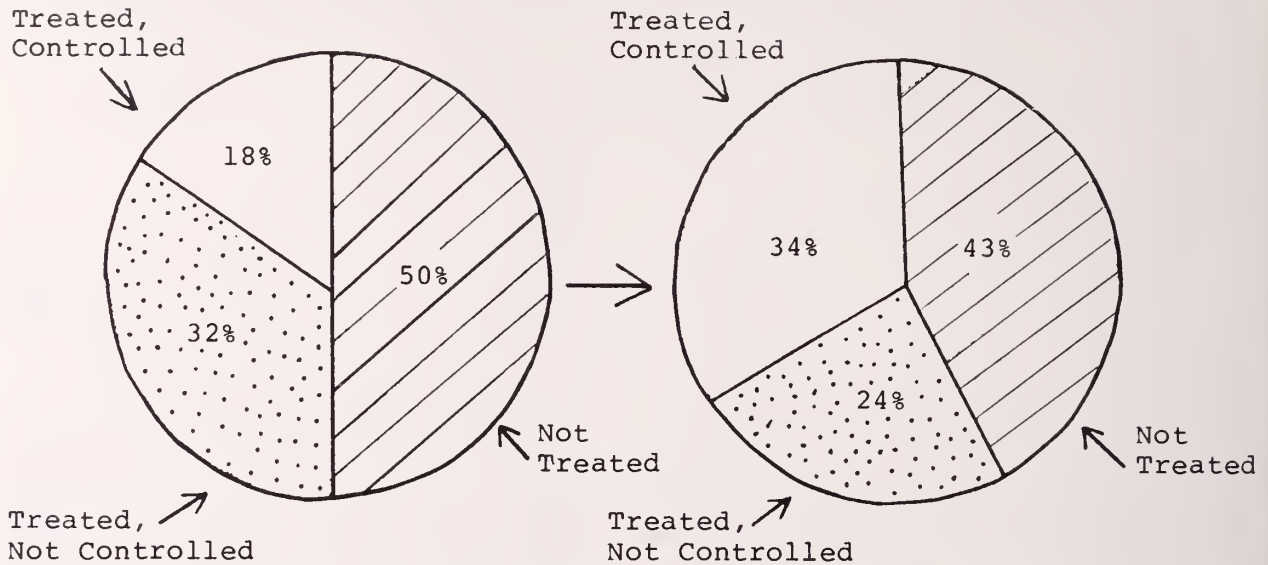
Many patients with initial HBP had either not returned for follow-up or had returned during the first few months of the Program but not recently. To clarify the outcome of patients for whom there was inadequate follow-up data, we reviewed the outpatient medical charts of 35 patients with untreated or inadequately treated HBP at the time of their last Program contact. Twenty-five patients had been seen by their physicians following their latest Program contact. In seven cases BP was not recorded in the chart for that visit. BP was normal without treatment in 5. Antihypertensive medication was increased in 4, begun in 3, and not changed in 2. Despite recorded elevations both at the center and in the doctors offices, HBP was not identified as a problem for 5 patients.

Telephone follow-up was used to reach hypertensive patients not recently seen by the Program. In four centers studied after 6 months of Program operation, 30% of patients hypertensive on their last Program contact had been reached by phone. Of these, 21% claimed to have seen their personal physician, and 42% returned for Program follow-up subsequent to the phone call. Of 63 patients with persistent HBP reached by phone, 60% had already seen their physicians (thereby complying with Program recommendation), and 43% returned for Program follow-up.

DISCUSSION

After one year in operation, what has the Program accomplished? Most exciting is the volunteer-staffed, area-wide network of regular free blood pressure centers. By reaching out to most area towns and major industries, one quarter of the areas's adult population has been screened for high

FIGURE 1: HBP CONTROL STATUS ON FIRST AND LATEST VISIT.



	FIRST		LATEST	
TOTAL*	992	100%	992	100%
UNTREATED	498	50%	422	43%
TREATED, NOT CONTROLLED	312	32%	238	24%
TREATED, CONTROLLED	182	18%	332	34%
* excluding proven labile hypertension.				

blood pressure. Used by many physicians and patients for regular follow-up, the centers help surmount some of the geographic and economic barriers to HBP control. Through mass media, health courses and group lectures, public and professional attention has been focused more than ever before on high blood pressure as a major health problem.

The challenges of HBP detection, treatment, and control are of similar magnitude in rural Maine as elsewhere in the United States (Table 2). The high incidence (50%) of elevated pressures on at least the first visit suggests a tendency for people at highest risk (known personal or family history of HBP, obesity, older age, etc.) to present themselves for screening.

Screening and public education are but means to the end of improved high blood pressure control. Changes observed in a large sample of hypertensives seen by the Program in its first 6 months suggest a considerable impact.

Comparing status on first and last Program contact, the number of patients taking medication for

high blood pressure increased by 15%. Of those with treated but still elevated pressure on first visit, 38% went on to achieve adequate control. Of those with well-controlled high blood pressure on first visit, 93% remained within normal limits. Excluding patients with documented labile hypertension, only 14% of hypertensive patients were well-controlled on first visit; on last contact, normal levels had been reached by 26%. The number of patients with adequate high blood pressure control thus rose by 82%.

The Program's greatest success and popularity has been with patients already diagnosed and under effective treatment prior to Program contact. Encouraged by their physicians to use the Program for follow-up, these patients have maintained a remarkable degree of HBP control (>90%).

Despite demonstrable improvement in blood pressure control, this study documented critical shortcomings in the Program as it originally functioned. The major deficiency was lack of effective follow-up. At the end of 6 months, only 15% of patients with initially untreated, non-labile high

blood pressure were known to have started treatment, and only 9% were known to have achieved adequate blood pressure control. Of those with initially mild-moderate elevations, 42% did not return to the Program for suggested re-check. Fully 80% of patients with initially marked hypertension had no further contact with the Program, and their actual outcome was not known at the time of the study.

The study clearly shows that, without subsequent prodding, many people will not comply with verbal and written instructions for follow-up. Nearly half of those advised to return for a free re-check did not do so, and more than a third of those advised to see a physician because of severe initial elevation had not done so at the time of telephone follow-up.

Since patients were not obligated to return to the Program for follow-up, Program records were not an accurate source of information regarding patient compliance. Many patients may seek physician evaluation promptly after the first elevation without waiting for Program confirmation. Other patients may disregard the initial elevation and seek neither Program nor physician re-check.

To more correctly assess the impact of this and similar programs and to determine which patients remain at high risk and in need of aggressive follow-up, patients and physicians must be contacted directly. Since the study, the Franklin County Program has increasingly emphasized patient follow-up. Over 400 telephone calls are made each month to patients whose HBP status is either unknown or unsatisfactory. These calls have been effective, prompting a return for Program recheck in nearly 50% of those called. Letters are mailed to those not reached by phone. Direct communication between Program and practicing physicians has been instituted in hopes that elevated blood pressures will not be lost in the hustle and bustle of busy practices. Person-to-person contact by visiting home health nurses is planned for refractory patients at high risk. For selected patients, screening results are sent directly to the patient's personal physician, who in turn is requested to assist in encouraging follow-up.

The success of this Program has depended in large part on the attitudes of local physicians. The Franklin County Program was sponsored by the hospital medical staff, and has been used by many local physicians for routine follow-up of known or sus-

pected hypertensives. Requiring three elevated readings prior to physician referral has helped prevent overload of physicians offices with borderline or labile elevations. Physician attitudes toward the Program will be reported subsequently.

The Franklin County Program has benefitted from the cooperative efforts of diverse community groups and individuals. The county hospital, private and group physicians, major industrial employers, civic and religious groups, an Army Reserve hospital, local radio station and newspapers, banks, and one-third of the area's adult population have worked together in a venture designed to improve individual and public health.

Volunteer effort, community cooperation, and physician acceptance have been necessary but not sufficient for Program success. Effective screening, follow-up, and educational efforts have required central coordination by part-time, paid personnel. Sporadic, uncoordinated screening without follow-up is an exercise in futility and should be avoided.

In summary, an effective, multifaceted high blood pressure detection and control program now serves the people of rural, west-central Maine. Community, industrial, and school screening will continue. Major educational projects will be incorporated into the local school curriculum. Patient follow-up will be improved, perhaps by use of computers and public health nurses. Formation of similar programs in other rural Maine areas will be encouraged. Funding for the ongoing Program will be sought from multiple sources. An attempt will be made to make the Program financially self-sufficient. All of this will be done in anticipation of improved high blood pressure control, with consequent reduction in cardiovascular morbidity and mortality.

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Updating of the Family Practitioner's Training

(A Customized Postgraduate Program at the Maine Medical Center)

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INTRODUCTION

Continuing medical education has long been the cornerstone of up-to-date quality medical care. It has been stated that within five to ten years of graduation from medical school virtually all the information about current medical practice gained during the medical school experience becomes obsolete. In accord with this reasoning and for other reasons of their own, various agencies, e.g., the specialty boards in family practice, state medical societies, and even individual medical groups are developing requirements for continuing medical education.

Many newer methods for providing continuing postgraduate education are being developed. Traditional sources such as journals, scientific meetings, specialty meetings, and formal courses conducted by medical school departments of continuing medical education are being augmented by multi-media approaches utilizing cassette tapes, slides, television, etc. Various mechanisms of awarding credit for time spent pursuing these activities are being developed. A different approach to postgraduate education is being developed in conjunction with the Family Practice Program at the Maine Medical Center in Portland, Maine.

MODEL

A two-week postgraduate experience developed by the authors to meet the need of one of the author's who is in Family Practice in rural Maine is described below. A tabular representation of that experience can be seen in Table 1.

Efforts were directed at learning experiences in two major areas with a service experience in a third. The senior author desired to become more familiar

with newer techniques in pulmonary and renal medicine and their application to his own clinical practice. Most of these newer techniques were available during the author's formal training, but were not being applied on a large scale clinically. Specific areas of interest in pulmonary medicine investigated were as follows:

1. Up-to-date treatment of acute respiratory failure utilizing blood gas analysis.
2. Experience with volume respirators and comparisons between these and pressure-cycled machines.
3. Observation of bronchoscopy with the fiberoptic bronchoscope.
4. The usefulness and application of office pulmonary function testing.

Areas of interest in nephrology were as follows:

1. Up-to-date criteria for dialysis and transplantation.
2. Management of these patients away from the Medical Center.
3. When to send patients for evaluation.
4. Feelings about the role of diet in the modern management of chronic renal failure.
5. Evaluation of the fees and technical problems of home dialysis.
6. Evaluation of the experience of a patient and a "technical partner" going through the training program once enrolled as prospective home dialysis patients.

In general, the acquisitions in the area of pulmonary medicine were of the type which would help the author practice better medicine at a considerable distance from the Maine Medical Center, while those experiences gained in the area of renal medicine improved the appropriateness of his referral practices.

A final learning experience was unrelated to the above. On the last day of the two-week experience, the Gastroenterology Department offered a special GI symposium. Because of the author's presence at the Medical Center, he could easily attend this symposium instead of participating in his usual daily activities.

As a member of the Family Practice Department, the author participated as an Attending at the Family Practice Unit on three afternoons during the two-week period. As an attending-teacher, he reviewed patients' problems with the Family Practice

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TABLE 1

MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY
FIRST WEEK				
A.M. Pulmonary Rounds Discuss Schedules Renal Rounds	A.M. Pulmonary Rounds Renal Rounds	A.M. Renal Rounds Pulmonary Rounds Medical Grand Rounds "Cardiomyopathy"	A.M. Pulmonary Rounds Renal Rounds Pulmonary Conf. Public Health Conf.	A.M. Pulmonary Rounds Renal Rounds
P.M. Family Practice Unit Attending	P.M. Library Time Pulmonary Rounds	P.M. Bronchoscopy Eve. Medical School Meeting Progress Report	P.M. Family Practice Unit Attending	P.M. Psyche Conf. Renal Rounds
SECOND WEEK				
A.M.	A.M. Renal Rounds	A.M. Pulmonary Rounds	A.M. Pulmonary and Renal Rounds	A.M. Gastro-Intestinal Conference
HOLIDAY	Respiratory Session Technical Aspect of Volume & Pressure Cycled Respsors	Medical Grand Rounds "Athrosclerosis"		
P.M.	P.M. Renal Rounds	P.M. Home Dialysis Unit Renal Rounds	P.M. Family Practice Unit Attending	P.M.

Residents who were seeing patients at the Model Family Practice Office.

DISCUSSION

The new American Board of Family Practice is the first specialty board to require re-certification. It is also almost certain to make a continuing education requirement part of this re-certification. The American Academy of Family Physicians (formerly the American Academy of General Practice) has, since its inception, required continuing education credit. For this reason it is logical that each family practice department have a strong commitment to continuing education. It should also provide a mechanism whereby busy practitioners can obtain continuing medical education. The visiting practitioner program provides an excellent opportunity for continuing medical education with benefits both to the practitioner and family practice program. For the Family Practice Program, it provides a vehicle for "preaching the gospel" of family practice to residents in training. It is a way of bringing some of the simpler and more pragmatic approaches into the training program. This program allows residents to see family practitioners who are truly enjoying their busy roles in many different communities. The practitioner accomplishes these ends as an attending in the Family Practice Unit by supervising and giving consultative support to the first, second, and third-year residents who are seeing patients in the Unit.

The Family Practice Department maintains a list of preceptors in various specialties at Maine Medical Center who enjoy participating in a visiting practitioner program. The department is also prepared to help define the needed skills, knowledge, and attitudes of the visiting practitioner and set up ap-

propriate schedules to fulfill these needs.

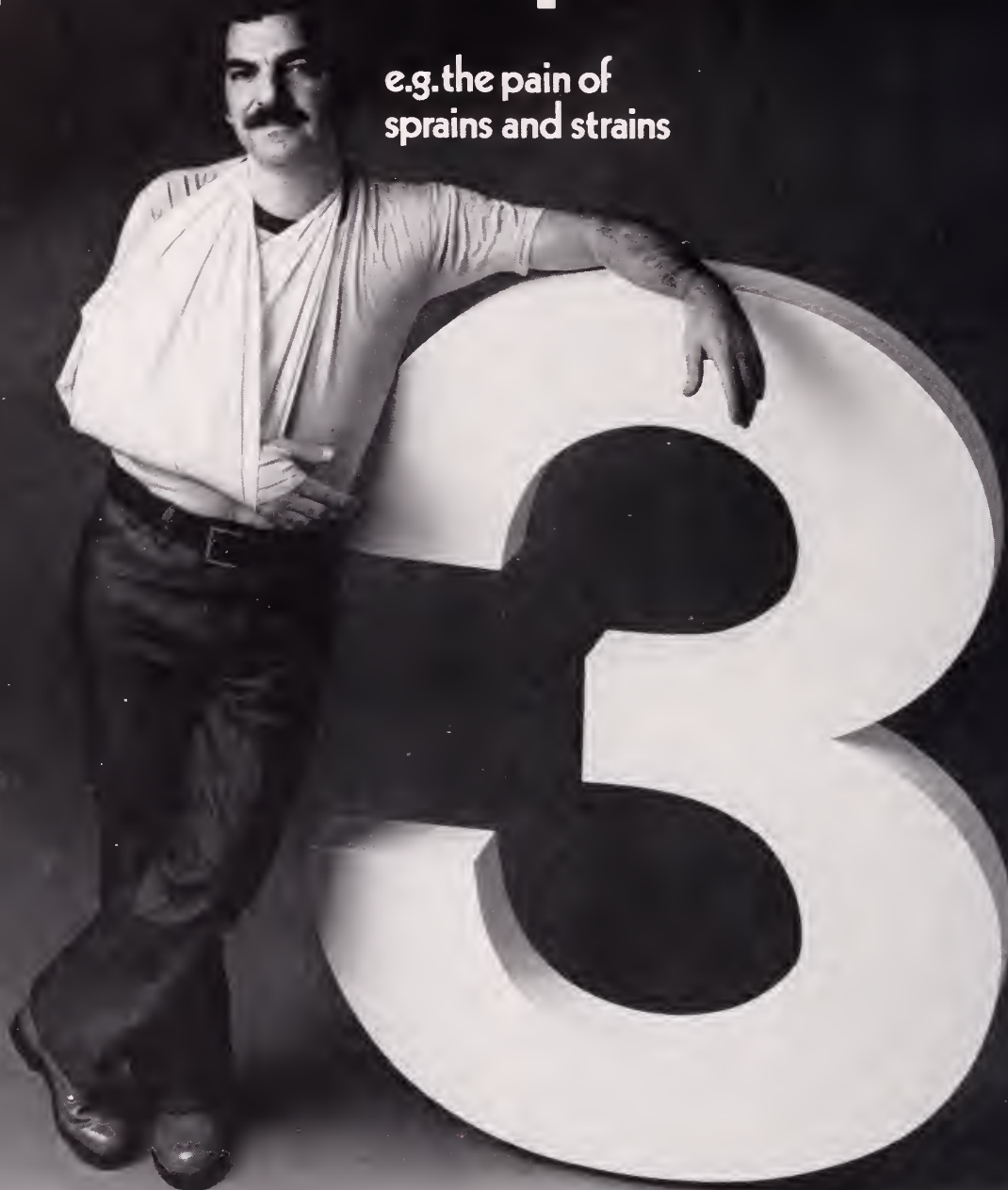
For the family practitioner wishing to participate in the program, several preliminary steps are necessary. First, he must decide how much time he can spend. Second, he must have in mind a relatively clear list of goals or objectives which he desires to obtain. Third, through the Department of Family Practice, he must make early contact with the prospective preceptors to a) further define the goals, b) set up a schedule acceptable and profitable to both, and c) obtain some sort of reading list to broaden the experience.

Scheduling is important in such a program. A longitudinal experience in more than one area simultaneously seems to provide greater exposure than does a series of segmental experiences over the same period of time. One seems to see more by doing renal and pulmonary together for two weeks than doing a week of renal then a week of pulmonary. Conflicts in scheduling become rampant, however. For this reason, it is suggested that one combine a rigid hospital-based experience such as nephrology with a more flexible office-based practice such as Rheumatology or Dermatology. Participation as an attending in the Department of Family Practice should allow the benefits to the program alluded to earlier. The visiting practitioner can also add considerably to the breadth and balance of family practice teaching seminars when co-directing such seminars with a specialist lecturer. The preceptors and visiting practitioner will both be expected to evaluate the program and make constructive criticism at the end of the period. Evaluation questionnaires to determine whether all initially defined objectives were attained is completed by the

Continued on Page 290

No. 3 As potent as the pain it relieves.

e.g. the pain of
sprains and strains



NOT TOO LITTLE

- as potent as the pain you need to relieve in patients with fractures, sprains, strains, wounds, contusions, and the pain of surgical convalescence
- unlike acetaminophen/codeine combinations, it does not sacrifice anti-inflammatory action

NOT TOO MUCH

- potent—yet not excessive
- addiction liability low

NOT TOO EXPENSIVE

- brand-name quality, yet reasonable in cost
- readily available in both hospital and local pharmacies

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- telephone Rx in most states, up to 5 refills in 6 months at your discretion (where state law permits)

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Trends in Education in York County

MELVIN BACON, M.D.*

For many years, I have been involved in professional and non-professional education in York County. Many programs have been arranged under my direction. These include programs for the laity, institutes and workshops for nurses, programs for the staff of the Goodall Hospital, and for the county medical society. We believe that here in York County, we have led the way educationally.

In the field of lay education, excellent programs have been conducted in this county, including Diabetes Detection and Diabetes Education Programs. We consider these endeavors among the best in the country. Over the years, 500,000 to 750,000 individuals have participated in these programs and I must add hundreds of new diabetics have been discovered. Additional programs have included "Health Fair in Wells, Maine,"¹ a class for retarded children in Sanford,² lectures on "Heart," "Hypnosis" and "Mental Health." Sanford was one of the first to enter into the field of Mental Retardation and Mental Health Education. The Charles Trafton Senior Citizen Center in Sanford, also has interesting Health Education meetings.

In the nursing field, our Institutes started many years ago under the sponsorship of the now defunct York County T.B. and Health Association and were continued by the Sanford-Springvale Community Health Association. These too were in a multiplicity of health fields. They were conducted annually in the month of October and were held from 7:00 p.m. to 9:00 p.m. on two to four consecutive Mondays. Attendance at these Institutes varied from 50 to 200 nurses. For the past three years, we have conducted one-day Workshops on Geriatrics, Stroke,³ Diabetes and Emergency Medicine. Attendance at these were from 100 to 200 nurses, and had the approval of the York County Medical Society and the Maine Medical Association. A novel idea was utilized and it concerned the opening of these meetings to student nurses from all over the State and also to senior pre-nursing students from several high schools in the county. This was done to expose the younger group to various aspects of nursing. These courses were held at Nason College, Springvale, Maine. Today, in addition, the Goodall, Webber and York Hospitals now have In-service Nursing Educational Programs. Another outstanding workshop on Respiratory Diseases was sponsored jointly by the Goodall Hospital, the Sanford-Springvale

Community Health Association and the Maine Lung Association. This was made possible through the efforts of George T. Nilson, S.M., M.P.H., Executive Director of the Maine Lung Association; Christine Hanscome, R.N., Respiratory Nurse Specialist, Maine Medical Center, Portland, Maine; Marolyn Roberts, R.N., Executive Director Administrator, Sanford-Springvale Community Health Association, Sanford, Maine; Gail Browning, R.N., In-Service Education Director, Goodall Hospital, Sanford; Elsie Doyle, R.N., Director of Nursing, Maine Stay Nursing Home, Sanford, and myself. Lest I forget, I should mention the York County Public Health Nurses who also have a monthly educational meeting in which I have participated.

With the cost of postgraduate medical education becoming prohibitive in many instances, I felt something should be done about it locally and we have. I can remember the day when outstanding speakers would come from Boston and elsewhere to speak at various meetings without compensation. They just welcomed the opportunity to get away from the big city. Now the pendulum has swung the other way. There are many good reasons I believe, despite the cost, where a medical school in Maine would be a distinct advantage and one of those would be in the availability of inexpensive but good postgraduate medical education in our State. Maine is no longer the "Backyard of Medicine." Please take no offense at this statement. It is my belief that this State has come into its own, medically speaking. There are many excellent and outstanding physicians and hospitals in our State.

Let me mention a few interesting additional examples of what we have done here educationally. On one occasion, we had a physician who was president of one of the larger drug companies who flew here from New York in his own personal plane to speak before our county society. On another occasion, we had one of the presidents of the American Medical Association speak. Other speakers have come from the Lahey Clinic, the Beth Israel Hospital, the New England Baptist, the New England Deaconess, Joslin Clinic, New England Medical Center, and other institutions to speak before the staffs and the county medical society. Other participants have been from the Maine Medical Center and the Mercy Hospital in Portland, the Veterans Administration Center in Togus, and the Central Maine General Hospital in Lewiston. I remember the day when most interesting courses were given at the Maine Medical Center at no charge and at the Central Maine General and St. Mary's Hospital in Lewiston at a most reasonable fee (this includes the Bingham Series).

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Let me at this point, describe a very interesting program that I believe few outside the county know about. Members of our county medical society and some from Portland, during the summer months, met at the toll gate in Kittery. There were a number of cars involved. We proceeded to Boston where we all met at the Beth Israel Hospital where we received an educational program including a tour of the hospital and observing in the Operating Room. This was set up especially for our group. We then had lunch at this hospital after which we went to the Booth Memorial Hospital (no longer in existence) where another excellent program was presented. From there we went to an excellent hotel where a social hour and a marvelous dinner was served. After this, the group attended a baseball game and returned to Maine a tired but well satisfied group. Similar programs were held for the staff of the Goodall Hospital in Boston.

Now to turn to our educational program⁴ at the Goodall Hospital. The following was our program for 1975-76. This represents a series of six meetings for six consecutive months starting in October and ending in March. These meetings were held either on Tuesday or Thursday evenings starting at 7:00 p.m. with a question and answer period following.

PROGRAM

1. Tuesday, October 21, 1975
Speaker — Peter Levine, M.D., Chief of Medical Division, Worcester Memorial Hospital, Worcester, Massachusetts
Subject — "The Diagnosis and Treatment of the Anemic Patient"
2. Thursday, November 20, 1975
Speaker — Yale J. Berry, M.D., Otolaryngologist; Associate Surgeon, Mass. Eye and Ear Infirmary; Surgeon, St. Elizabeth Hosp., Brighton, Mass.; Assistant Clinical Professor, Tufts Medical School and Clinical Instructor, Harvard Medical School
Subject — "The Diagnosis and Treatment of Common Problems in Otolaryngology, Rhinology and Laryngology"
3. Tuesday, December 16, 1975
Speaker — Larry G. Anderson, M.D., Rheumatologist, Maine Medical Center, Portland, Maine
Subject — "Autoimmune Disease"
4. Thursday, January 22, 1976
Speaker — Lawrence Eron, M.D., Fellow in Infectious Diseases, Massachusetts General Hospital, Boston, Massachusetts
Subject — "The Use and Abuse of Antibiotics-Diagnostic Criteria"
5. Tuesday, February 17, 1976
Speaker — Kenneth H. Gabbay, M.D., Department of Endocrinology, The Children's Hospital Medical Center, Boston, Massachusetts
Subject — "The Diagnosis and Treatment of the Diabetic Child and Its Complications"
6. Thursday, March 18, 1976
Speaker — Seymour Zimble, M.D., Associate Professor of

Orthopedic Surgery, Tufts University School of Medicine, New England Medical Center Hospitals, Boston, Massachusetts

Subject — "The Diagnosis and Treatment of Common Orthopedic Problems"

We had no problem in securing excellent speakers. This was the fourth year in succession we have conducted this program. The programs are accredited by the American Academy of Family Practice through the Maine chapter. This year, we are going one step further. We are going to apply for accreditation of our program by the Maine Medical Association and the American Medical Association. In addition to this, plans call for the conducting of CPCs, case presentations, X-Ray conferences monthly, tapes, TV video tape presentations and films. In addition, a list of educational TV programs of interest to physicians will be compiled. Plans to beef up our library by addition of new books and subscriptions to journals will be carried out. Telelectures is another possibility and also inter-hospital television network including the hospitals in York and Cumberland Counties, if it becomes available, as is going on in other parts of the State. Other avenues will be explored. All these plans are contingent on requirement for accreditation by the American Academy of Family Practice, the Maine Medical Association and the American Medical Association. It would be presumptuous of me not to mention that the Webber and York Hospitals also conduct programs for their physicians.

SUMMARY

This paper, in brief, presents some facets of education in York County and Sanford including the Goodall Hospital, for the laity, physicians and nurses. We believe that we have led the way educationally. This should set an example for others to follow.

ACKNOWLEDGEMENTS

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Maine Blue Cross and Blue Shield News

PHYSICIANS' OPINION SURVEY: PART I

In an effort to better define physicians' attitudes towards Maine Blue Shield, a group from the Research and Provider Affairs Department developed a "Physicians' Opinion Survey" during March of 1976. The survey was distributed at county medical society meetings during the months of April and May. It was also distributed to the following committees: Osteopathic State Peer Review, Osteopathic Insurance, Maine Medical Association Committee on Health Care Financing, and the Maine Medical Association Advisory Committee on Health Care Financing. At the same time, a letter was distributed to all physicians informing them that we had drafted a survey. A few physicians requested and received a copy of the survey as a result of this letter.

Of the 270 surveys distributed, 80, or 30%, were returned. The following is the first half of a rough tabulation of the survey results.

Asked to rate the three types of Blue Shield contracts, indemnity, 80% UCR, and full UCR, as well as a negotiated schedule used by other Plans, the respondents saw UCR as being most favorable, followed by a negotiated schedule and 80% UCR.

Seventy-five percent of the respondents favored a single statewide area for determining UCR fees.

Fifty-six percent felt that the statewide approach would either lower or have no effect on fees. Twenty-five percent felt that a statewide area would raise fees.

Sixty-nine percent felt that the idea of relating periodic increases in UCR maximums to the Consumer Price Index of other economic indices was good.

The Service Benefits provision for low income Blue Shield subscribers was viewed favorably by 50% of those surveyed, while another 10% had no opinion. Forty percent did not like the concept.

Most of those surveyed felt that the Service Benefits income limits for Blue Shield "C", Blue Shield "D", and 80% UCR were about right, while between 11 and 16% felt they were too high.

Most of the respondents did not know what percentage of Blue Shield payments were made on a Service Benefit basis. Of those who gave an answer, a predominance felt that the figure fell somewhere between less than 5% to 10%.

Eighty percent felt that when their office staff telephoned Maine Blue Shield, the service is generally adequate to good. Only 10% saw it as inadequate.

Correspondence between Maine Blue Shield and offices was seen by 76% as being adequate to good, while 10% felt this service to be inadequate.

When a Blue Shield representative calls on a respondent's office, he most often (50%) sees the nurse or office staff and sometimes (29%) sees both the nurse and physician.

Sixteen percent felt they would like to see a Professional Relations representative 4 times a year, 24% 2 times a year, and 43% said they would like to see a representative on request only.

The final part of the survey results will appear next month.

News, Notes and Announcements

THE DEPARTMENT OF POSTGRADUATE MEDICINE
OF
ALBANY MEDICAL COLLEGE
announces

**Reservations Now Being Accepted for the Eighteenth
Postgraduate Medical Seminar Cruise
February 7-18, 1977**

An eleven-day cruise from Miami, Florida, aboard the luxurious ss. STATENDAM of Holland-America Cruises.

Ports of call include Willemstad, Curacao; LaGuaira (for Caracas) Venezuela; St. George's, Grenada; Bridgetown, Barbados; Fort-De-France, Martinique; and Charlotte Amalie, St. Thomas.

Faculty of the Albany Medical College will present a shipboard postgraduate program emphasizing medical topics of particular interest to general internists, and family practice physicians.

Albany Medical College of Union University is accredited by the Council on Medical Education of the American Medical Association to offer courses in continuing medical education. The seminar is acceptable for credit toward the Physician's Recognition Award.

Request has been made to the Commission on Education, American Academy of Family Physicians for approval of the program for continuing education study credit.

For information write to: Frank M. Woolsey, Jr., M.D., Department of Postgraduate Medicine, Albany Medical College, Albany, New York 12208.

UPDATING OF THE FAMILY PRACTITIONER'S TRAINING — *Continued from Page 285*

family practitioner after completion of his program and six months later. A final area to be established involves the awarding of credit hours spent in such a program. At some time in the future, it is hoped that as the program develops it may be possible to have the practitioner liberated from his office by having the Family Practice Unit supply a supervised resident to cover the practitioner's duties at his home base while he is on study leave at the Medical Center.

CONCLUSION

In this age of increased emphasis on continuing education, new methods are being developed to deliver this education to the consumer, the busy

practitioner. One such program, the visiting practitioner program, is discussed here. Returning to the Medical Center as a means of continuing medical education is a useful and feasible alternative. To do this the participant must have a clear idea of his objectives. He must also contact those who will act as his preceptors in advance of his participation. He should have a schedule and a reading list. This type of program provides certain advantages. It enables precise shaping-up of one's weaknesses and provides a real close personal contact with reliable consultants who may be of help in the future. Finally, it brings some amount of non-academic medicine's simple pragmatic approaches back to the Medical Center Training Programs.

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The Neonatal Intensive Care Center*

JOHN C. SERRAGE, M.D.

The Neonatal Intensive Care Center (NICC) has been in operation for three years. This paper reviews what has been done in the three years and presents plans for the future. The unit was created for the intensive care of the high risk newborn and to improve the neonatal mortality rate in Maine. Infants requiring more than normal newborn care, i.e., the high risk babies, can be defined in terms of numbers or diagnosis. Formulas have been devised for calculating the number of babies needing this increased care. It is estimated that 2% of live births need intensive care. Using 14,000 as the birth rate in Maine, the number requiring intensive care is 280. It is also estimated that 3% of live births, or approximately 420 babies for an average year, need intermediate care. A formula also exists for calculating the incidence of Hyaline Membrane Disease. Fifteen per thousand live births would give an incidence of 210 cases of HMD per year in Maine.

Another way of defining the high risk infant is by diagnosis. Table 1 is a list of conditions which are used by many intensive care units as indications for referral. We in Maine have emphasized the importance of transferring the infants with respiratory distress needing high oxygen, frequent blood gas determinations and respiratory support; extreme low birth weight infants weighing less than 1250 grams; and infants requiring general or cardiac surgery. The other conditions on the list require intermediate care and the need for transfer depends upon the capabilities of the referring hospital. Transfer may also be made to a closer hospital.

The intensive care unit contains 12 incubators and a treatment station and is capable of caring for six infants on respirators. The unit is people. Physicians are available in the unit or nearby 24 hours a

TABLE 1

WHOM TO TRANSFER

A complete list of candidates to be considered for possible transfer would include cases of:

- a. Birth weight less than 1,500 grams
- b. Gestational age less than 34 weeks
- c. Infants of diabetic mothers
- d. Neonatal Seizures
- e. Suspected sepsis, meningitis, etc.
- f. Persistent cyanosis without respiratory distress
- g. Congenital anomalies requiring observation for neonatal surgery

day. The nurse-patient ratio is 1:1 or 1:2 on the sickest infants around the clock. There is a nurse educator responsible for training new nurses and offering continuing education to the other nurses. Parents are encouraged to visit because it is important for them to establish a positive relationship with these sick infants. There is an increased incidence of battering of graduates of neonatal intensive care units, possibly related to a maternal-child relationship disturbed by untimely and prolonged separation. The unit is equipment. Each infant has heart rate, respiratory rate or both monitored continuously. The rocking chair and the famous music box are also in use to provide the necessary human touch. The unit is ancillary services — chemistry, hematology, blood gases, radiology available 24 hours a day. The transportation of the infants to the center is now the responsibility of each referring hospital and many of the ambulance services used are not adequate.

The following are some of our statistics accumulated over the past 2 years: 280 admissions in 1974 of which 141 were transferred; 345 admissions in 1975, of which 190 were transferred. These figures compare favorably to the calculated figures discussed previously. Table 2 shows our results with Hyaline Membrane Disease. The death rate from this disease in our unit has been 20% for the last two years.

*Presented by the Departments of Obstetrics-Gynecology and Pediatrics, Maine Medical Center, Portland, Maine at the annual session of the Maine Medical Association on June 7, 1976 at Rockport, Maine.

TABLE 2

RESPIRATORY DISTRESS SYNDROME TREATED AT THE NICC			
Year	Total Cases	Deaths	Mortality Rate
1972	23	11	48%
1973	36	6	16%
1974	81	19	23.5%
TRANSFERRED	56	12	21.4%
MMC	25	7	28%
1975	75	15	20.0%
TRANSFERRED	61	14	23%
MMC	14	1	7%
Total Admissions to the NICC			
1974	280	(141 transferred)	
1975	345	(190 transferred)	

of these infants. Two of them had died. One was a crib death, a condition which has an increased incidence in the small pre-term infant. The other died of bronchopulmonary dysplasia, another hazard of the intensive care era. Three of the 33 were not developing normally, but only one of them was severely retarded. Eighty-five percent of the infants found were normal at one year of age.

Several conclusions can be drawn from all these statistics. Improving obstetrical care is most important in improving neonatal survival. The incidence of RDS can be reduced with this improved OB care by (1) better timing of the delivery; (2) de-

TABLE 3

LOW BIRTH WEIGHT MORTALITY STATISTICS							
500-999 1 # 2 oz.-2 # 3 oz.				1000-1499 2 # 4 oz.-3 # 4 oz.			
Year	Born	Died	% Died	Born	Died	% Died	Total % Died
53/62	83	78	94%	108	60	55%	72%
63/72	75	69	92%	94	33	35%	60%
1973	6	6	100%	11	5	45%	65%
1974	24	17	71%	31	8	26%	46%
1975	16	10	62%	34	7	20%	34%

This compares favorably with rates in major medical centers and compares with a 45-50% death rate in the immediate pre-intensive care era. If the deaths from HMD in babies born at MMC are extracted from this data they show a steady decline: eleven in 1972 for a death rate of 48%; 5 (of the 6) in 1973 for a death rate of 33% (a transitional year in terms of the care given these infants); 7 in 1974 for a rate of 28%; and 1 death from HMD (out of 1500 babies born at MMC in 1975) for a death rate of 7%.

Our Low Birth Weight statistics are in Tables 3 and 4. The accepted rates in the pre-intensive care era were a 95% mortality for babies weighing less than 1000 grams (2 lbs. 3 oz.) and 50% mortality for infants weighing from 1000 to 1500 grams (2 lbs. 3 oz. to 3 lbs. 4 oz.). Our present rates show great improvement and compare favorably with the current rates in major centers. One third of the infants below 1000 grams are now living as compared with essentially none before intensive care and two thirds of the infants in the 1000-1500 gram category are now living. Before intensive care two-thirds of them were dying. In Table 4 note that in 1975 our ability to save the extreme low birth weight infant with Hyaline Membrane Disease (RDS) was still about the same as in the previous year (50%) but the RDS rate has decreased (from 51% to 28%) and our ability to save the extreme LBW infant *without* RDS has improved greatly (51% to 26.5%).

The final group of statistics concerns our follow-up on the condition of these small infants at one year of age. We had 50 babies who a year ago either weighed less than 1500 grams or had been on a respirator. We were able to contact 33, or two-thirds,

TABLE 4

LOW BIRTH WEIGHT INFANTS TREATED AT THE NICC (less than 1500 grams)		
	1974	1975
With RDS	28 (51%)	16 (28%)
Died	11 (40%)	8 (50%)
Without RDS	27 (49%)	34 (72%)
Died	14 (51%)	9 (26.5%)
Total	55	50
Total died	25 (46%)	17 (34%)

laying the delivery in some cases; (3) stopping labor in some; (4) a judicious premature delivery in other cases before the baby is severely compromised in utero; (5) maturing selected fetuses with Celestone®; and (6) improved resuscitation techniques in the delivery room. We can also conclude from the previously discussed statistics that the incidence of extreme low birth weight infants probably will increase in the future, but these infants will be in better condition, not asphyxiated, will not develop RDS, and more will live and remain neurologically intact.

Another conclusion which can be made is that the transport system must be improved. At the present time, each individual hospital is responsible for transporting its own babies and, therefore, many small hospitals transport very infrequently. It is difficult for these hospitals to keep up their skills at transporting or to train nurses to do this job. A regional transport system is needed. This can be achieved by placing transport equipment in several central locations and training nurses and ambulance services in those locations. Teams could then go out

to nearby smaller hospitals on request and pick up sick infants, delivering the ones requiring intermediate care to the regional hospital and those requiring intensive care to the NICC. A map of the deliveries in Maine shows that 4500 deliveries would be served by such a service in the Portland area, 2000 in the Lewiston area, 2700 in the Waterville-Augusta area, 2300 in the Bangor area and about 1000 each in the Aroostook, Down East, and Mid-Coastal areas.

Two problems must be overcome before such a system can be implemented. How can these regional hospitals staff their nurseries so that a nurse can be suddenly removed for several hours at a time, and how should the nurses' salaries be funded when they are tending an infant in an ambulance? We have to convince the third party payers that a more sophisticated transporting system is a legitimate part of the sick infant's care. By decreasing acute and chronic morbidity, the total cost of medical care will be decreased. We at the NICC are prepared to train these nurses and ambulance personnel. We need the organized cooperation of all hospitals, physicians, third party payers and ambulance services to make this program effective.

If all the proposed improvements in care take place: improved obstetric care, improved delivery room resuscitation techniques, improved transport of sick infants, intermediate care in regional hospitals — predictions can be made concerning the type of patients we will be seeing in the NICC in the future. The surgical patient with congenital anomalies will continue, reduced somewhat by genetic counselling, prenatal diagnosis and planned parenthood. There will continue to be some Hyaline Membrane Disease patients, but fewer than previously and treated more successfully with improved survival. Finally, there will be increased numbers of extreme low birth weight infants in whom we are recognizing an entirely new set of problems. Most of them have apneic spells which require respiratory support. All have immature GI tracts and are difficult to feed. We have used nasojejunal feedings, hyperalimentation and intravenous fat solutions. We are already seeing these small infants in our unit. Our smallest surviving infant weighed 700 grams at birth, is now 4 months old and appears to be developing normally. A second 700 gram infant is now one month old and still in the unit.

Maine Medical Center, Portland. Maine 04102

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Polymyalgia Rheumatica*

LARRY G. ANDERSON, M.D.

In our day-to-day practices, you and I prefer caring for certain diseases more than others. Our favorite diseases are likely to be those we can do something about — diseases for which treatment is available and effective and even dramatic in improving a patient's life. In rheumatology, one clear example of such a disease is polymyalgia rheumatica. The features of polymyalgia rheumatica should be known by every clinician who deals with patients in the older age group, for missing *this* diagnosis is a real disservice to the patient. Polymyalgia rheumatica is a fairly common problem. We see at least one new case each month, and in the community there are surely many patients with this illness going unrecognized and untreated. Like so many other diseases, the diagnosis of polymyalgia rheumatica is fairly easily made if the doctor is aware of the disease and recognizes his patient's description of the very suggestive symptoms. The tip-off is in the history.

The features of polymyalgia rheumatica are illustrated in Table 1. This is a disease of older patients. The diagnosis should not be seriously considered for anyone under 55 years of age, and most patients are in their 60's and 70's. The syndrome of proximal myalgias is distinctive. Typically, as patients complain of pain and aching and stiffness in a symmetric distribution about the shoulder and hip girdle muscles, they run their hands over their necks, shoulders, upper arms, low backs, buttocks, and upper thighs. The symptoms usually clearly localize to muscle rather than to joints and tendons. The pain tends to be worse at night so that sleep is disturbed, and severe morning stiffness is a prominent complaint. Often, aggravation of myalgias by use or exertion suggests claudication. Rising from a chair or bed may be such a difficult task that polymyalgia rheumatica is severely debilitating. In fact, we have seen patients bedfast with the disease, some being unable even to turn in bed. In addition, there may be remarkable constitutional symptoms such as fatigue, anorexia, weight loss, fever, and depression.

Another important clue to the diagnosis is a normal physical examination. The physician may be confronted with a concerned but not very ill-appearing patient who, in spite of bitter complaints of muscle pain, has no objective abnormal findings in the muscles or joints. Hence, the unwary physician may feel quite comfortable in attributing the vague muscular symptoms, as well as weight loss, to depression in an elderly patient.

If the index of suspicion is present, however, the

TABLE 1

DIAGNOSIS OF POLYMYALGIA RHEUMATICA

1. *Age*: 55 or older
2. *Symptoms*: proximal, symmetric myalgias without weakness, with constitutional symptoms
3. *Physical exam*: normal musculo-skeletal system
4. *Laboratory*: ESR 50 or higher (Westergren). Anemia.
5. *Therapeutic response*: dramatic to low dose steroid
6. *Exclusions*: infection, RA, SLE, malignancy, polymyositis
7. *Self-limited disease*: remission after about 2 years

alert physician will perform the next critical step, a simple one of obtaining a sedimentation rate. The sedimentation rate is markedly elevated in this disease, certainly far out of proportion to the paucity of physical findings. The Westergren sedimentation rate should be more than 50 and is often greater than 100. Other nonspecific laboratory findings include a moderate anemia with hematocrit in the low or mid-30's and a low serum albumin. Otherwise, the laboratory is of no value except to exclude other diseases, such as infection, rheumatoid arthritis, systemic lupus erythematosus, malignancy, or polymyositis.

The diagnosis of polymyalgia rheumatica, then, is suggested by the age of the patient, the characteristic proximal muscle symptoms, the paucity of physical findings, and the strikingly elevated sedimentation rate. The diagnosis is further supported by a dramatic therapeutic response to low doses of corticosteroids. Prednisone in doses as low as 10 mg daily should bring about considerable and prompt subjective relief of pain and stiffness. Some patients have described complete amelioration of symptoms within twelve hours of the first dose, and many experience their first good night's sleep in months. More typically, the myalgias gradually lessen over a few days and, objectively, the sedimentation rate falls and the anemia is corrected in the first week or two of treatment. Larger doses of steroids have been advocated but we prefer starting low, to achieve greater specificity of the therapeutic response. Other diseases in the differential diagnosis will also respond to steroids, but none so dramatically and quickly to low dose steroids as polymyalgia rheumatica.

The final criteria for the diagnosis of polymyalgia rheumatica is the termination of symptoms and no further need for steroids after the disease has run its course. Polymyalgia rheumatica is a self-limited illness, with duration ranging from six months to four or more years and averaging about two years.

Polymyalgia rheumatica is usually easily distinguished from other diseases. Table 2 compares polymyalgia rheumatica and polymyositis. There is

*Presented by the Department of Rheumatology, Maine Medical Center, Portland, Maine at the annual session of the Maine Medical Association on June 7, 1976 at Rockport, Maine.

TABLE 2

DIFFERENTIAL DIAGNOSIS OF POLYMYALGIA RHEUMATICA VS POLYMYOSITIS		
	<i>Polymyalgia Rheumatica</i>	<i>Polymyositis</i>
Muscle discomfort	+++	0
Muscle weakness	0	+++
Muscle tenderness	±	+
Muscle atrophy	0	+
Abnormal muscle enzymes	0	+
Abnormal electromyogram	0	+
Abnormal muscle biopsy	0	+

TABLE 3

DIFFERENTIAL DIAGNOSIS OF POLYMYALGIA RHEUMATICA (PMR),
RHEUMATOID ARTHRITIS (RA) AND SYSTEMIC LUPUS
ERYTHEMATOSUS (SLE)

	<i>PMR</i>	<i>RA</i>	<i>SLE</i>
Proximal myalgias	+++	+	+
True joint discomfort	±	+++	++
Morning stiffness and gelling	++	++	+
Fatigue	+	+	+
Fever	+	±	+
Synovitis on examination	Transient if at all	+++	++
Joint limitation or deformity	0	+	0
Subcutaneous nodules	0	+	0
Sedimentation rate elevation	+++	++	++
Anemia	+	+	+
Rheumatoid factor	0	+	0
Antinuclear antibodies, LE cells	0	0	+

a striking contrast between subjective and objective findings in these diseases. The patient with polymyalgia rheumatica has prominent symptoms but no objective evidence of muscle disease by examination or laboratory, while the patient with polymyositis usually does not complain of muscle discomfort but has pronounced muscle weakness on examination and has abnormalities of muscle enzymes, electromyogram, and muscle biopsy. The most difficult differential diagnosis is usually between polymyalgia rheumatica and early sero-negative rheumatoid arthritis (Table 3). Rheumatoid arthritis may present with a myalgic syndrome, and both diseases have morning stiffness and elevated sedimentation rates. Usually patients with rheumatoid arthritis have more prominent joint symptoms, and, of course, objective joint findings and a positive rheumatoid factor point to the correct diagnosis.

There is a large overlap between polymyalgia rheumatica and giant cell arteritis or temporal arteritis. Although there is still considerable uncertainty and controversy about the exact relationship of polymyalgia rheumatica and giant cell arteritis, we feel there is a common disease spectrum such that all patients with polymyalgia rheumatica probably have underlying giant cell arteritis. This concept is supported by autopsy studies and clinical investigations in which about one-third of patients with polymyalgia rheumatica have positive temporal artery biopsies, even in the absence of symptoms of temporal arteritis per se. The symp-

TABLE 4

CLINICAL PRESENTATIONS OF POLYMYALGIA RHEUMATICA AND GIANT CELL ARTERITIS	
Proximal myalgias	Facial pain
Morning and night stiffness	Mastication claudication
Weight loss, anorexia	Trismus
Fatigue	Dysphagia
Fever	Tongue blanching
Night sweats	Arm or calf claudication
Lethargy, apathy, depression	Peripheral neuropathy
Headache	Cerebrovascular accident
Visual loss	Myocardial infarction
Any visual disturbance (blurring, scotomata, diplopia)	Myocarditis, congestive heart failure
Temporal or scalp tenderness or nodules	Dissecting aneurysm Unexplained anemia

TABLE 5

GOALS OF TREATMENT

1. Achieve and maintain symptomatic relief until disease has run its course.
2. Keep ESR normal.
3. Use lowest possible dose of steroid that will achieve first two goals.

PREDNISONE TREATMENT SCHEDULES

1. Polymyalgia rheumatica: 10 mg. q.d. or q.o.d. initially, with gradual adjustment to maintenance.
2. Giant cell arteritis: 40-60 mg. q.d. initially with tapering to maintenance.
3. Maintenance: Lowest dose that will suppress signs of giant cell arteritis and symptoms and keep ESR WNL.

toms of giant cell arteritis depend upon the end organ of involved arteries (Table 4). In addition to the muscular and constitutional symptoms already mentioned, patients may present with headaches or visual symptoms including sudden blindness. Even more catastrophic complications include cerebral vascular accidents or myocardial infarctions. Giant cell arteritis may involve any artery large enough to be named, such as ophthalmic, temporal, middle cerebral, or coronary arteries.

Prednisone is the treatment of choice in polymyalgia rheumatica. The use of corticosteroids is clearly justified in this illness in view of 1) the relatively low dose of steroids required to control the disease in most circumstances; 2) the fact that the illness is self-limited and one is not committed to steroids for the life time of the patient; and 3) the fact that steroids can avert the severe complications of giant cell arteritis when the disease is adequately controlled. The goals and guidelines for treatment are outlined in Table 5. One would expect the required steroid dose to decrease as the disease runs its course until the time comes when a patient has been tapered to a dose such as prednisone, 5 mg every other day, and the steroids can be stopped.

In summary, if you are on the lookout for this disease in your practice, we think you will see it. The most important point is that polymyalgia rheumatica is a completely treatable disease than can be easily missed. The prematurely incapacitated and very uncomfortable older patient with this disease

may be astounded at the good results of your treatment, and you may save him from blindness or other serious complications of giant cell arteritis. Few

other rheumatic or any other disease can be so gratifying to treat.

180 Park Ave., Portland, Maine 04102

Teenage Pregnancy†

DAVID D. YOUNGS, M.D.,* and JENNIFER R. NIEBYL, M.D.**

DIMENSIONS OF THE PROBLEM

During the past decade, there has been a startling increase in the number of adolescent pregnancies. In 1972, 1 out of every 10 girls became pregnant while still of junior or senior high school age. Coupled with the falling birthrate in the United States, their numbers have become even more conspicuous. Until recently, teenage pregnancy was thought to be a problem confined primarily to the nonwhite, lower income inner city population. Recent information indicates that teenage pregnancy is involving more and more middle class youngsters in both rural and suburban settings. For example, in Arizona, during 1971, 18.9 percent of all births were to teenagers 16 years or under, of whom 63 percent were white.¹¹ Klein reports that illegitimacy rates for middle class whites is rising while the rates for blacks continue to fall.⁹ For many of these youngsters, marriage is no longer a prerequisite to parenthood; nor is adoption the only alternative. Currently no more than 18 percent of unwed mothers give up their newborn infants for adoption.¹⁷

Earlier reports by Battaglia and Coates suggest that adolescents fare less well obstetrically, and that those 14 years and under are at particular risk for major complications such as toxemia, anemia, prematurity, prolonged labor, and postpartum complications.^{2,3} More recent studies by Dwyer and Webb fail to show significant differences in obstetric complications or outcome for adolescents when "more comprehensive" obstetric care was provided.^{5,15} While pregnant adolescents continue to represent a special group at risk, differences in access to quality care, social class, and racial back-

ground are probably more significant factors than age alone in influencing obstetric outcome. An additional consideration is that adolescents are a heterogeneous group even when social class and ethnic background are similar. For example, the pregnant 12 year old, who is dependently attached to her mother and inexperienced in social relationships, represents a very different management problem from the sophisticated 17 year old, who is sexually experienced, and comes shortly after a missed menstrual period for a therapeutic abortion.

In practical terms, then, physicians who provide care for pregnant adolescents must acquire a degree of sophistication about adolescents in general, a flexibility of approach, and a willingness to deploy a variety of therapeutic strategies in dealing with this often difficult age group. In communities that lack physicians who are interested in the problem, attendance for prenatal care will usually be poor, obstetric complications excessively high, and repeat pregnancy the rule rather than the exception.

ETIOLOGIC FACTORS

The successful management of the pregnant adolescent depends upon some working knowledge of the social and psychological forces as well as the family dynamics that set the stage for the teenager's pregnancy. For middle class adolescents, pregnancy is commonly the result of maladaptive attempts to solve psychological conflicts specific to their particular stage of adolescent development.⁷ For example, loosening of a dependent relationship with a clinging mother, "acting out" an erotic attachment with a seductive father, or manipulating a reluctant boyfriend into a more committed relationship are common dynamics. When serious psychological or social pathology is responsible for teenage pregnancy it is more often associated with other maladaptive patterns such as drug abuse, delinquency, abandonment by the family or truancy from school.

Intrafamily dynamics may be the motivating force in a significant number of such teenage pregnancies. Using a comparison group of nonpregnant teenagers, Abernethy has demonstrated that adolescents who become pregnant are more likely to be dissatisfied with their mother as a role model, express a preference for their father even to an exclusive

†Revised version of *Adolescent Pregnancy and Abortion*. Medical Clinics of North America, Vol. 59, No. 6, Nov. 1975.

Presented by the Departments of Obstetrics-Gynecology and Pediatrics, Maine Medical Center, Portland, Maine at the annual session of the Maine Medical Association on June 7, 1976 at Rockport, Maine.

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degree, or report hostility within the parents' marriage.¹ In contradistinction, parents who are affectionate and close are more likely to foster their daughter's identity as a woman and enhance her self esteem, thus diminishing the probability of promiscuous sexual behavior and possible conception.¹

Ignorance about sexual functions and superstitions or fears concerning the use of contraception also contribute to the problem of unwanted pregnancy. A small proportion of adolescents actively desire pregnancy and probably an equal number are indifferent about the possibility of pregnancy following coitus. For some of these youngsters, pregnancy may represent a constructive attempt to negotiate the developmental problems of adolescence. Unfortunately, the odds are very much against the development of a stable marriage for such teenagers or the creation of a healthy environment for the newborn infant, although some young mothers do succeed. Factors which appear to be central in those who succeed include (1) the presence of a caretaking person who will provide the necessary emotional and financial security until the adolescent is self sufficient, (2) a realistic view of the maternal role as well as the needs of the infants, and (3) the motivation for pregnancy being for positive and healthy reasons rather than self-destructive or neurotic ones. An appreciation of the personal, family and social factors impinging on the pregnant adolescent is helpful in orienting the physician to the alternatives available in managing the pregnancy and to the opportunities for "planning" future pregnancies. Successful care, then, will depend on understanding the various etiologic factors involved, the specific needs of the adolescent, and the availability of various community resources.

GOALS FOR THE CARE OF PREGNANT ADOLESCENTS

The question of quality obstetrical care for the pregnant adolescent must address itself to considerations that go beyond the narrow definition of traditional medical services. The increased rates of fetal and maternal morbidity previously alluded to have not been shown to be significantly altered merely by the provision of traditional obstetrical services; therefore, any successful effort must embrace a broader range of personal and health care needs for this group. With this in mind the realistic goals for quality care are (1) early diagnosis and intervention, (2) early and active participation in a suitable health care program, (3) an opportunity for therapeutic abortion as an alternative, (4) attention to the social and personal needs of the adolescent, (5) health education, particularly in the areas of human sexuality, reproduction and contraception, (6) preparation for mothering activities and introduction to child development and child care, (7) coordinated follow up care as well as family planning services, and (8) reintegration of the adolescent mother back into her community through such as-

sistance as day care, vocational or special educational services.

MODEL PROGRAMS: ELEMENTS OF SUCCESS

Osofsky and Sarrel were the first to report on a successful interdisciplinary approach to adolescent pregnancy. Focusing predominantly on low income nonwhite adolescents, they were able to achieve a remarkable reduction in obstetrical morbidity, prematurity, and antenatal complications as well as lowering the incidence of repeat pregnancy and increasing school attendance.^{13,14} Subsequent reports from a more diverse population including white middle class youngsters show similarly good results.¹⁵ Drawing from our own experience with an interdisciplinary approach to teenage pregnancy¹⁶ and those reports in the literature,^{8,13,15} the common attributes of such programs that seem to be major contributors to success are: (1) improved communication between community, school, and medical services leading to early diagnosis and referral and complementary rather than competitive care, (2) the selection of nonjudgmental professional and staff members who are interested and skilled in relating to pregnant teenagers as people rather than as problems, (3) the inclusion of psychological and social work services as an integral part of obstetrical care rather than following the traditional patterns of referral that imply "there is something wrong with you, therefore you must see the psychiatrist or social worker," (4) providing continuity of medical care by an interested obstetrician, nurse midwife, nurse, or other experienced staff member who offers a more permanent relationship throughout the antepartum period, labor and delivery, and postpartum experience, (5) follow-up care for the new mother and infant that combines vocational, educational, and social work services in addition to inter-conceptual medical care for the mother and well baby care for the infant, (6) providing easy access to a nonjudgmental professional who is available to coordinate ongoing care, assist in handling common adjustment problems, provide advice about child care, or make necessary alterations in the contraceptive program.

MANAGEMENT CONSIDERATIONS: THE CONSULTANT VERSUS THE PRIMARY CARE ROLE

Prompt and accurate diagnosis is a prerequisite to the successful management of adolescent pregnancy. Awareness of the increasing frequency of pregnancy among teenagers, particularly in the middle class, should alert the physician to the possibility of pregnancy among his young female patients. Vague symptoms such as nausea, fatigue, abdominal cramps, or syncope should not be dismissed until the question of pregnancy is explored. Establishing the date of the last menstrual period will frequently be helpful in suggesting the diagnosis. The necessity for a "high index of suspicion" should not be confused with an intrusive or probing

manner. In spite of most adolescents' anxiety and apprehension during the first office visit, usually sufficient "clues" are provided to suggest the possibility of pregnancy.

The initial encounter of the adolescent with the physician and the office staff is of critical importance. A sense of security and confidence is slow to develop among adolescents, even in the best of circumstances. In the face of an embarrassing problem (pregnancy) and on unfamiliar territory (the physician's office) the initial encounter may determine whether the patient will return for regular care or abandon the physician for less adequate services. Several visits may be required before the patient feels sufficiently secure and trusting of the physician to provide an accurate history and allow a complete and informative pelvic examination. The initial office visit, then, for the young female adolescent is of major importance. It may be her first pelvic examination. Along with the usual mixed feelings of anxiety and fear, the uncertainty of possible pregnancy commonly makes her more sensitive to minor slights, thoughtless criticism, or unsympathetic handling. Advising abortion or adoption *before* a comfortable and honest rapport with the physician has developed may seriously strain the doctor-patient relationship or more likely result in failure of the patient to return.

A skilled office staff may ease the adolescent's anxiety, obtain a more complete history or serve as an accessible friend during this difficult period. Guidance and advice concerning contraceptive information, abortion, or adoption may be more easily accepted from office staff members of the patient's own sex or someone closer to her age. When the physician also cares for the adolescent's mother, issues of confidentiality and trust are more difficult to deal with and referral to a sympathetic colleague may be preferable. When the patient is accompanied by her mother in the initial visit, a useful approach is to meet briefly with both to collect relevant information from the mother and observe firsthand the mother and daughter interaction. In addition, it is helpful to get some sense of the father's reaction to his daughter's pregnancy. Fathers that accompany their daughters for the first interview can be handled in much the same manner as the mother. The majority of the interview time should be spent with the adolescent, obtaining her history, gaining her confidence, and establishing a secure relationship. Only when the adolescent is markedly immature, retarded, or severely disturbed should the primary relationship be developed with the mother. The initial history and physical examination, including the pelvic examination, should establish the presence of pregnancy or make it a strong possibility. Waiting for uterine enlargement or a positive pregnancy test only delays an open discussion of possible pregnancy and unnecessarily postpones a review of such options as abortion. Several visits may be required to satisfactorily explore the patient's feelings about

abortion versus continued pregnancy or to rally the support of the family.

Common complaints of pregnant adolescents seen in the office include feeling hurried, embarrassed, being treated like children, or being advised that "abortion is the only solution." For many adolescents, particularly those 16 years of age or older, pregnancy is not associated with serious social or psychological pathology. However, in younger patients who are separated from their families, truant from school, or demonstrate evidence of delinquent behavior, psychiatric disturbances or major adolescent adjustment problems should be suspected and referral for appropriate mental health counseling is indicated. Physicians who are sufficiently experienced and interested may elect to provide the majority of the adolescent's health services including informal counseling, patient education, and routine antenatal care. Other physicians may elect to refer the patient to a colleague, a teen clinic or other community based program that has particular expertise with this problem. In either case, the physician who has a comfortable and familiar relationship with school personnel and relevant social agencies will improve the adolescent's chances of successfully resolving her pregnancy.

PREVENTIVE HEALTH MEASURES

Pregnant adolescents can be viewed as a group at particular risk for repeated pregnancy⁴ as well as future social, vocational, academic, and health care problems. Infants who are the product of adolescent pregnancies are likewise at risk for a wide range of developmental problems including child abuse, child neglect, retarded physical and emotional development, poor school performance, and serious delinquent behavior.⁶ No single approach has been efficacious in dealing with the entire range of problems presented by the pregnant adolescent. Success for the majority of patients appears to be related to the degree to which quality obstetrical, pediatric, social, psychological and educational services are provided. For repeated pregnancies among adolescents, the prematurity rate approaches fifty percent.

Health education during pregnancy which focuses on the issues of sex education, emotional and attitudinal preparation for pregnancy, family planning, nutrition, drug effects on pregnancy, preparation for delivery, planning for the baby, infant care, and family life can be extremely valuable in helping the adolescent to integrate her many experiences. Educational programs that offer psychological assistance as well may promote more responsible and mature behavior. The adolescent's contacts with the professional staff during pregnancy may be her only good source of information concerning sexuality, venereal disease, and/or contraception. Her future willingness or ability to use contraception or seek care for suspected medical problems will depend to a large degree on her experiences with the medical staff during pregnancy and the availability

of sympathetic professional people afterwards. When family planning and contraceptive services are provided in the more traditional fashion, the adolescent's continued participation in such programs has been discouraging.¹⁰ More promising results of continued contraceptive usage are found when the broader emotional and health care needs of these young mothers are provided.⁸ Clearly, the success of the "storefront" health clinics with pregnant adolescents suggests the need for establishing more comfortable and informal milieus in caring for teenagers. In more traditional institutions separate teen clinics run by selected staff personnel have also been very popular. For example, a program for some 400 pregnant adolescents at Johns Hopkins Hospital was able to enroll the majority (60 percent) of patients by the twelfth week of pregnancy with excellent continued participation. In addition, 95 percent of the patients have returned for postpartum care.¹⁶

CONTRACEPTION

Contraceptive counselling and services are important for the adolescent. It is currently estimated that 1.4 to 2.3 million single female teenagers in the United States need contraception.¹² Whether the young woman is sexually active or not, there is opportunity for education about her reproductive organs, ovulation, and menstruation. A discussion about how women can prevent unwanted pregnancy can follow naturally from such a conversation.

Unfortunately, no contraceptive has proven clearly superior for any population, including teenagers. The risks of birth control methods must be compared with the alternative of an unwanted pregnancy. Selection of the most appropriate contraceptive continues to be a difficult issue. Most teenagers, however, can make an appropriate decision after they have been informed about the various methods, their risks, side effects and failure rates.

Oral contraceptives are the most effective form of birth control if the patient has sufficient motivation to take a daily pill. In addition they offer the teenager with dysmenorrhea the advantage of pain relief. A small risk of pituitary suppression exists, but the more common clinical problem is the teenager who misses a few pills and presents with an unwanted pregnancy.

The newly designed smaller intrauterine devices are often well tolerated by nulliparous as well as parous teenagers. The patient must be cooperative, however, to allow accurate insertion and avoid the risk of uterine perforation. The most frequent side effects are increased menstrual flow, inter-menstrual bleeding, and cramps; consequently, they are not usually recommended for patients who already have significant dysmenorrhea. Most problems with the intrauterine devices occur in the first few months. For patients who retain the device the pregnancy rate is in the 2 percent range. Thus, the IUD removes the potential for patient failures in-

herent in the use of oral contraceptives, but introduces a small percentage of method failures.

A mature teenager may be educated to use a diaphragm and use it reliably, but failure to regularly use the device threatens the success of most teenagers to use a diaphragm or condom contraception.

Missed periods are common in adolescents in whom regular ovulatory menses have not become established. It is important, however, to perform a pelvic examination and a pregnancy test in such cases since many a pregnant adolescent has concealed her pregnancy from her parents and physician.

CONCLUSION

Adolescence for most young people represents a time of considerable change and uncertainty. When this developmental period is compounded by unwanted pregnancy, the experience may be particularly trying to the patient as well as her family and physician. Psychological struggles are frequently intensified by family instability, the lack of appropriate adult role models, or inadequate information about human reproduction, sexuality, and/or contraception. All too often adolescents are left to fend for themselves among peers who are equally uninformed about sexual function and reproductive matters. For many youngsters, the family physician continues to be the only visible source of reliable and confidential help. Coordinated interdisciplinary services are probably the most effective approach and can more economically meet the multiple needs of this group. When such services are not available, adequate care can be provided by the interested physician who is willing to set aside the necessary time, provide a sympathetic ear, and develop some expertise in dealing with this challenging problem.

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Life and Death Decisions In Rheumatology*

ROBERT A. SYLVESTER, M.D.

Three situations arise in the patient with rheumatoid arthritis which can cause sudden emergencies. The three problems involve 1) The cricoarytenoid joint, 2) The cervical spine, and 3) The knee. The cricoarytenoid joint is a true synovial joint connecting the two cartilages which are important in the function of the larynx in phonation and respiration. During normal phonation, these joints allow a gliding motion so that the arytenoid cartilage comes together and separates thus adducting and abducting the vocal cords. The incidence of cricoarytenoid involvement in rheumatoid arthritis is between 25 and 50%. The symptoms of cricoarytenoid arthritis are sensations of foreign body in the throat, hoarseness, tightness in the throat, nocturnal stridor, and occasionally laryngeal stridor.

Acute laryngeal involvement with stridor and respiratory obstruction is an emergency. This can at times be the first manifestation of rheumatoid arthritis. Usually, however, the stridor occurs as a complication superimposed on the cricoarytenoid arthritis such as an acute flare-up or a complication of an acute infectious bronchitis.

Examination by indirect laryngoscopy during the acute phase will show reddening and swelling of the cricoarytenoid joint with some edema of the cords. Chronic changes will show fixation of the arytenoids with a narrow airway. With normal inspiration, the arytenoid cartilages rotate and separate the cords. In the chronic case, they are fixed. The vocal cords remain adducted.

The treatment is local injections of steroids into the cricoarytenoid joints, and temporary tracheostomy. Cricoid joint involvement should alert the physician to possible problems with intubation, and acute infections which can cause a flare-up of the cricoarytenoid arthritis and subsequent respiratory insufficiency.

The second situation in the rheumatoid patient which can cause an emergency situation involves the cervical spine. The cervical spine in rheumatoid arthritis is involved in 25% of cases. This condition is important because there is a possibility of damage to the spinal cord which can cause severe neurologic deficits and death. The odontoid process forms two synovial joints, one anteriorly with the atlas, and

one posteriorly with the transverse ligament of the atlas. The stability of the alanto-odontoid joint depends largely on the transverse ligament which passes behind the odontoid process and keeps it firmly in contact with the anterior arch of the atlas. The proximity of the synovial tissue to the odontoid process and in the ligaments render the ligaments liable to erosion and weakening by rheumatoid granulation tissue. When there is laxity of erosion of the transverse ligament, two complications may arise. Pressure on the spinal cord by the odontoid process or pressure on the vertebral arteries by C-1. Clinically patients complain of occipital headaches, paresthesias, and vertigo. The normal x-ray of alanto-odontoid process will show a distance not exceeding 2.5mm. Subluxation of the odontoid process will show a distance of greater than 2.5mm. The treatment consists of immediate immobilization with a cervical collar, and if necessary surgical fixation of the atlas.

The third medical emergency which occurs in a patient with rheumatoid arthritis involves the knee. Rheumatoid effusions of the knee may be complicated by development of large popliteal cysts — the so-called Baker's cyst. These cysts are connected to the main joint space and originate as a herniation either directly from the joint or via a communicating bursa in the popliteal space. Baker's cyst can rupture into the calf and cause severe pain, and mimic phlebitis. The diagnosis of a ruptured Baker's cyst can be made by arthrogram studies.

A case presentation will demonstrate this point. The patient came in complaining of pain in his right calf. Examination revealed a medial bulge and severe tenderness. The patient had injection of dye into the right knee which showed dye going from the Baker's cyst into the calf. The patient was treated with aspiration and injections with Depo-Medrol® and recovered without any sequelae. It is important in patients who do have rheumatoid arthritis and complain of calf pain that ruptured Baker's cyst be considered.

In summary, in the patient with rheumatoid arthritis, one should be aware of the possibilities of medical emergencies such as cricoarytenoid arthritis causing laryngeal stridor, and respiratory insufficiency; cervical spine subluxation with subsequent paralysis, and ruptured Baker's cyst with possible misdiagnosis of phlebitis.

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Commiserate And Cop-Out Or Cure: The Common Miseries*

PHILIP P. THOMPSON, JR., M.D.

An older physician in Portland, some 40 years ago, had the perfect formula for success. He had three telephone answers for requests that his patients made of him. If they said, "Doc, I have a pain in the chest," he would answer, "meet me in the hospital in 5 minutes — goodbye." If they said, "Doc, I have a pain in the belly," his answer was, "meet me in the hospital in 1 hour, goodbye." If it was colic or some pain that would pass within an hour they would either not show up or they were satisfied they were cured. If the pain had persisted, they would be at the hospital ready for an operation. Generally they were operated upon. If they said, "Doc, I have a pain in the neck — back — or extremity," he would answer, "heat, rest and aspirin, goodbye."

Since he was primarily a surgeon, he further improved on this formula by owning the hospital, so he could not lose. The patient was more than satisfied and at that stage of medical knowledge he had the best chance of cure no matter what ailed him.

In 40 years there have not been many improvements of these three prescriptions. Perhaps his retort to the request for relief of musculo-skeletal "diseases" might be today "cold, rest and codeine" instead of "heat, rest and aspirin." However, that would mean that he would have had to add "meet me in the hospital." His financial return for such a visit compared to a 30 day hospital stay with an M.I. versus a surgical fee and hospital stay of 20 days would scarcely have been worth his time.

Today few of us could use all of his formulas for "cures," yet we still have nature working for us and should capitalize upon it whenever we can. This is particularly true of the musculo-skeletal "miseries" where 80% of the complaints are related to trauma and will heal themselves. The physician must intervene to allow the healing process to occur and prevent the patient from further injuring himself by persisting in his daily routine.

Musculo-skeletal disorders fall into five general categories: 1) acute traumatic, 2) chronic traumatic, 3) entrapment and compartmental syndromes, 4) inflammatory and degenerative joint diseases, 5) ischemic vascular syndromes, 6) miscellaneous inflammatory and tension problems such as viral myalgias and fibrositis or "psychogenic rheumatism." Of these, most are curable not because of physician intervention but because they cure them-

selves. The physician can give the patient the impression he was "cured" by allowing this process to occur in the least possible time.

- 1) *Acute traumatic injuries:* "cold, clamp, and codeine" is the 3 "C" easy formula for cure.

Cold may be applied locally with ice — in a "baggie" or for more prolonged periods and less messily by cold pack with a commercially available "Kold Kompess.[®]" This contains a polymer which holds the cold as "hydrocollator" holds the heat.

The clamping can be done by splinting the extremity with heavy towels, thermal plastics, ace bandages or tape. The firmer the part is "clamped" to prevent all motion — the less pain and the quicker the healing. Splints are best — they can be removed and reapplied easily by the patient himself. A must in any "clamping" therapy is not to have it so tight as to interfere with circulation and to remove it daily to allow maximum full range of motion short of pain or interference with the healing process.

Codeine — (not aspirin or other analgesics) or opiates should be given in sufficient amounts to relieve pain satisfactorily. This varies with patient pain threshold and extent of the injury. Generally physicians don't prescribe opiates enough. Let the opiate fit the pain in drug, dosage, and frequency. Prescribe according to what you would require yourself if you had similar injury or pain.

- 2) *Chronic trauma* — The "dis-eases" associated with chronic trauma are generally occupational and recreational. Each of these is so much a part of peoples' lives, or they seem so routine to each individual that unless the physician asks for specific details of these aspects of the patient's life the etiologic significance may be overlooked. The stressful nature of each may vary from day to day so it may be necessary to inquire into the specifics of recent events. For example — the housewife who has to iron for hours at a time when all eight of her children come home from school vacation, or the tennis player who has eight matches to play on a weekend to get into the finals or a 100 pound girl who has her first "heavy date" with a 250 lb. football tackle. Each of these activities could result in a patient seeking relief in your office a day or two later.

Just as there is an inflammatory reaction when

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blood is being absorbed in acute traumatic conditions, similarly there is inflammation associated with chronic trauma. For this reason anti-inflammatory drug dosages of analgesics are required in the treatment of these conditions.

Therapy consists of 1) aspirin-like drugs, especially aspirin, 2) local injection of anesthetics and/or steroids, 3) and restraint from the provocative stress. This might be called S.A.P.P. program (*steroids-aspirin-prevent provocation).

Aspirin should be given regularly and in sufficient dosage to have both analgesic and anti-inflammatory effect for 5 days. At least 12 (0.3gm) tablets of ASA a day are sufficient to get salicylate levels above 20. Comparable doses of Butazolidin® 600-800 mg a day, Indocin® 150-200 mg a day. All are given in four divided doses starting on awakening — ending at bedtime. They will have side effects primarily on the GI tract so the patient should be warned of bleeding and ulcer symptoms. If the medication is not taken with meals, it should be taken with a full 8 oz. glass of milk or water and if any GI symptoms occur — follow each dose with appropriate dose of antacid.

If the above first 5 day regimen does not produce "cure" then the next step is the use of steroids locally if a "trigger point" or points of pain can be identified. Usually with bursitis, epicondylitis, tenosynovitis or fibrocytis a maximum point of tenderness can be located.

The appropriate steroid can be mixed or be proceeded with the injection of 2-5ml of lidocaine or carbocaine using a 22 gage needle, preferably disposable, of appropriate length. Short acting steroids such as Decadron® should be used for acute traumatic conditions — while the longer acting steroids such as Depo-Medrol®, Aristospan® or Hydreltra T.B.A.® are used for conditions with an inflammatory element. Multiple site injections of the total dose are usually more likely to "cure."

Ethyl chloride spray as "Frigiderm®" may be very effective for bursitis fibrositis, myositis, non-specific syndromes with diffuse muscle aching. It can be applied by an intelligent family member. It is sprayed from a distance of 2 feet in a sweeping motion covering 4-6 inches per second.

Greatest care should be taken not to cause blanching or freezing of the skin. It may require 15-20 minutes of spraying for pain relief. Active motion of involved muscles accompany spraying. Care must be taken to prevent inhalation of ethyl chloride.

If the above measures do not work, a short 2-3 day course of systemic steroids in the form of oral prednisone — 20 mg a day, may be "curative."

- 3) *Entrapment and compartmental syndromes* are most commonly manifest as "carpal tunnel" and "shin splints." Compartmental syndromes result from increased tissue pressure within a fibrous non-stretchable muscle compartment often in the forearm, hand or lower leg. If conservative measures of splinting and local injection of steroids (for carpal tunnel only) do not give relief, or is severe pain, sensory loss or motor weakness is present, surgical release is indicated as an emergency measure.

It is not within the scope of this paper to discuss the other three categories — 4) inflammatory and degenerative joint disease, 5) ischemic vascular syndromes and 6) miscellaneous generalized inflammatory and tension musculo-skeletal problems. However, with the newer understandings of mechanisms of disease and orthopedic surgical techniques we are learning how to control and cure many of the previously "incurable" skeletal disorders.

In conclusion — a few specific "miseries" and their specific treatments will be outlined.

MISERY	TREATMENT
"Trigger Finger"	Inject - long acting steroid into nodule
"Carpal Tunnel"	Splint & NSAID - Non steroidal anti-inflammatory drugs
"Wry Neck"	Splint with folded bath towel - ice collar - Valium® and sufficient codeine.
"Tennis Elbow"	Good wrist support & NSAID - inject - surgery
"Dequervains"	Splint thumb, inject steroid - surgery
"Coital Crunch" (Tietze's)	Reverse position - towel binder - exclude MI
"Housemaid's Knee"	Off knees - inject steroid
"Morton's Toe" (Neuralgia)	Wider shoes - metatarsal bar - surgery
Painter's Nodules	Get off the ladder - use staging
Mason's Knees	Knee pads - aspirate - inject steroid
Shin Splints	Elevate, rest - surgical decompression if sensory or motor loss develops

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Low Back Pain*

CURRIER MCEWEN, M.D.

Low back pain, often associated with pain referred to the leg, is one of the commonest musculoskeletal complaints and often one of the most difficult to cope with especially in patients who welcome an excuse to be unable to work or when the possibility of litigation or compensation is in the background. A list of what I consider the more important causes is shown in Table 1 in which the more common ones are marked with asterisks.

The first two are sometimes listed together under the heading of sprain but in my opinion they are quite distinct. The pain of acute low back sprain is sudden in onset and the patient usually remembers what he was doing when it occurred. It can be thought of as similar to a sprained ankle. In contrast, the pain of low back strain is insidious in onset and is related to muscle fatigue and spasm. This type of chronic low-grade pain can, of course, be punctuated by a superimposed acute sprain. As indicated in the table, low back strain may be of postural origin as in the individual with "dorsal round back" or may be due to obesity or to occupational causes. In the slender individual, the center of gravity in the standing position is directly down the axis of the vertebral column and the upright position is maintained with minimal strain on the muscles of the back. When, however, the center of gravity is shifted forward appreciably by the weight of an obese, overhanging abdomen the back muscles are under constant stress to maintain the erect posture. Occupational causes of low back strain usually are of postural type.

Regional and localized inflammation of connective tissue structures is less easily pinpointed in the back than in the shoulder area but inflammation of muscles, tendons and ligaments undoubtedly is a common cause of back pain. Indeed most of the pain of acute sprains and chronic strains is due to inflammation secondary to those mechanical causes just as is, for example, tendonitis at the shoulder. Localized inflammation due to infection and chemical irritation is possible but probably is extremely rare.

Herniated discs and degenerative disc disease are well known causes of low back pain. Radicular referral of pain to one or both legs can occur with any of the causes of low back pain but is a particular hallmark of these disc derangements. The acute onset of pain due to a herniated disc is readily explained by pressure on the nerve radicles by the extruded or protruded disc material. The more insidious pain of degenerative disc disease is less sat-

TABLE 1

CAUSES OF LOW BACK PAIN

* ACUTE LOW BACK SPRAIN
* CHRONIC LOW BACK STRAIN: POSTURAL — OBESITY OCCUPATIONAL
* REGIONAL SOFT TISSUE INFLAMMATION MYOSITIS TENDONITIS
* DEGENERATIVE DISC DISEASE
* HERNIATED DISC
* ARTHRITIS: * ANKYLOSING SPONDYLITIS - * OSTEOAR. METABOLIC BONE DISEASE * OSTEOPOROSIS HYPERTHYROIDISM OSTEOMALACIA PAGETS DISEASE
INFECTIOUS SPONDYLITIS: TUBERCULOUS - OTHER TUMORS - * MALIGNANT - BENIGN - OSTEOID OSTEOMA "COMPENSATIONITIS"

isfactorily explained. In some instances, posterior osteophytes associated with the disc degeneration can actually cause pressure on the radicles. Such cases are stubborn and extremely difficult to deal with and fortunately are rare. In the more common cases, there probably is no actual pressure but there is less space in the foramina through which the radicles pass due to the narrowing of the discs; and this combined with inflammation and edema probably is the explanation of the radiculitis with its characteristic referral of pain.

Two forms of arthritis must be thought of in the differential diagnosis, namely, ankylosing spondylitis and osteoarthritis. The former is readily recognized in advanced cases by the stiff back and x-ray demonstration of syndesmophytes and damage or obliteration of sacroiliac joints. In early cases one must depend on the clinical features, the development of sacroiliac changes in serial films taken at six month intervals and a positive test for HLA-B27¹ (formerly HLA-W27).

Osteoarthritis of the spine is distinct from degenerative disc disease and refers to degenerative arthritis of the diarthrodial apophyseal joints. Undoubtedly it occurs but it is difficult to demonstrate and its role as a cause of low back pain is hard to assess since degenerative disc disease is present also.

Of the various types of metabolic bone disease of the spine, osteoporosis is by far the most common and important. When a vertebral crush fracture is shown on x-ray, pain is easily explained. I have become convinced, however, that severe osteoporosis of the spine can cause pain even without actual fracture. Possibly this is caused by irritation of pain endings in the periosteum or medulla due to stress from the soft bone; or perhaps it is the result of chronic muscle strain.

Tuberculous spondylitis, once so common a cause of back pain, needs scarcely to be con-

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sidered today. Other infections such as those due to pyogenic microorganisms and brucellosis can occur but are extremely rare.

Malignancies with metastases to the spine are a very significant cause of back pain today. Malignant and benign chord tumors and osteoid osteomas are other causes of severe pain.

The last item in Table 1 is shown as "compensationitis". The importance of pending litigation or assessment for compensation in affecting the patient's symptoms and course is too familiar to require extensive discussion. In my opinion actual malingering is rare. However, even the most self-reliant and honest patient can scarcely avoid having his symptoms exaggerated subconsciously by the pending possibility of compensation benefits.

It is apparent that a number of causes listed in Table 1 are imperfectly understood as to their pathogenesis and that they overlap considerably. Fortunately, pinpointing which of them is primary in an individual patient usually is not crucial for the basic plan of treatment is the same for most. In the remainder of this article, I will outline that basic program and will then discuss some particular additional measures required for some.

Table 2 summarizes the regimen of treatment which I follow in patients with low back pain. Clearly the immediate need is to relieve pain. Because most instances of low back pain are quite obviously due to mechanical causes, most programs of treatment prescribe the use of analgesics. This, I believe, is a serious error because the pain almost always is related to inflammation. Nothing in medicine could be more mechanical in its cause than a sprained ankle but within a very short time the ankle presents all the cardinal signs of inflammation: pain, tenderness, swelling, erythema and local heat. So it is with the mechanically induced low back pain. Therefore, the first measure is to put the patient at rest in a non-sagging bed and start anti-inflammatory medication. Because the corticosteroids are the most potent antiinflammatory agents which we have and it is essential to reduce deep inflammatory edema as quickly as possible, this is the medication of choice provided the patient does not have an infection, tuberculosis, peptic ulcer or other contraindication. My practice is to give 5 mg. tablets of prednisone by mouth four times daily for two days and reduce the dose by one tablet every two days so that it is stopped after eight days. In the case of a very large person or extremely severe pain, one may start with six tablets daily. At the same time that the prednisone is begun, I have the patient take 3 or 4 aspirin tablets four times daily and this is continued after the prednisone is stopped and is kept up until all pain has subsided. Indomethacin or one of the more recent non-steroidal antiinflammatory agents may, of course, be used instead of the aspirin if experience shows it to be more helpful in the individual patient. In this connection, let me emphasize that acetaminophen is

TABLE 2

TREATMENT OF LOW BACK PAIN
1. RELIEF OF INFLAMMATION AND PAIN
a) ANTIINFLAMMATORY AGENTS:
PREDNISONE
ASPIRIN
NEWER MED.
b) ANALGESICS
c) LOCAL PROCAINE - CORTICOSTEROID
2. BED REST - FIRM BED - SHORT TERM
3. ELIMINATION OF PAINFUL ACTIVITIES
4. WEIGHT LOSS IN OBESE PATIENTS
5. THERAPEUTIC EXERCISES - NON-WEIGHT BEARING
6. BACK SUPPORT
7. GRADUAL RESUMPTION OF ACTIVITIES
8. LONG RANGE RECONDITIONING PROGRAM
9. PSYCHOLOGICAL SUPPORT
10. SURGERY
DISC
SPINAL FUSION

merely analgesic and not antiinflammatory and hence not a suitable substitute for aspirin. If pain persists in spite of antiinflammatory medication, an analgesic agent may be added. Even morphine may be prescribed if pain is extremely severe but should not, of course, be continued longer than two or three days. In practice, analgesics are not often required. As to so-called muscle relaxants, I have never known them to be of benefit. If a localized area of particular tenderness is present, deep infiltration of the area with a mixture of procaine and a long-acting corticosteroid is well worth trying.

Continuing with the items in Table 2, bed rest is advisable at the start making sure that the patient's bed does not sag. A thick foam rubber mattress with a bed board under it eliminates all sagging yet conforms to the body contours and serves admirably. I must emphasize that whereas bed rest often is needed at the start, treatment of low back pain usually is best carried out on an ambulatory basis after the first few days.

The patient must, of course, refrain from activities which cause pain. Therapeutic exercises designed to stretch the hamstring muscles and strengthen both flexors and extensors of the back should be started cautiously on a non-weight bearing basis as soon as pain is relieved but should be stopped at once for the time being if pain returns.

No spinal brace, however heavy or rigid, can immobilize the back and I am convinced that heavy braces do more harm than good. A lightweight support, however, can be helpful. A molded support no wider than the back made of a thermoplastic material and slipped into the pocket of a cummerbund-like elastic belt about 12 inches wide held together in front with a Velcro fastening is easily and quickly made.² Such a support does not immobilize the back any more than therapeutic collars do the neck yet like the latter they are helpful.

When the patient is fully recovered, it is time to start the gradual resumption of milder activities which formerly were painful and at this time also it

is imperative to start a long-range reconditioning program of therapeutic exercises. The patient who has once had an episode of low back pain is vulnerable to a recurrence and the long-range program, faithfully carried out, can do much to prevent this.

The heading "psychological support" in Table 2 is used to include whatever reassurance the individual patient may need. Wise assurance and guidance throughout the period of treatment may help prevent the patient's preoccupation with possible compensation benefits which often interferes with normal recovery.

Surgical removal of protruded disc material with or without local spinal fusion may be required in patients with herniated discs but only in the presence of serious neurological deficits, intractable pain not relieved by the general program which has been outlined or repeated recurrences.

Whereas the basic program outlined above meets the needs of most causes of back pain listed in Table 1, there are several for which it is only partly appropriate, namely, ankylosing spondylitis, osteoporosis, infectious spondylitis and some tumors.

In ankylosing spondylitis, the first step is to reduce inflammation and pain but in this disease corticosteroids are seldom used because both indomethacin and phenylbutazone appear to be the drugs of choice. Therapeutic exercise of stretching type carried out daily for many years can do much to help maintain good posture.

The treatment of osteoporosis remains a difficult and controversial subject with estrogens, supplemental calcium and vitamin D, and sodium fluoride

each having its supporters. In view of accumulating evidence that therapy with estrogens increases risk of endometrial cancer, they must be used in low doses and with caution.³ Since physical activity slows the development of osteoporosis, the basic program outlined in Table 2, omitting the prednisone, also is helpful and should be started early.

If the painful back is due to an infectious process, corticosteroids are contraindicated and an appropriate antibiotic should be used. In the case of tumors, treatment varies, of course, depending on the type of neoplasm.

SUMMARY

The more frequent causes of low back pain and a regimen of treatment have been briefly presented. A major factor which is often overlooked in the pathogenesis of low back pain is inflammation. Although in most instances the precipitating event is a mechanical one, secondary inflammation supervenes. Hence antiinflammatory medication usually is more helpful than analgesics.

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Reminder to M.M.A. Members

CONTINUING MEDICAL EDUCATION ACTIVITY REPORT

The bylaws of the Maine Medical Association were amended in June of 1973 as follows: Chapter I, Section 11, — "Each member of the Maine Medical Association shall be required to report his activities in continuing medical education every year according to a format provided by the Committee on Continuing Medical Education."

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Please fill in your activity report promptly and return to the M.M.A. office, P.O. Box 250, Brunswick, Maine 04011.

The Pharmacology and Therapeutic Use of Antihistamines

VINCENT J. CIRILLO, M.S. and KENNETH F. TEMPERO, M.D., Ph.D.

ABSTRACT

This review discusses: (a) the biosynthesis, metabolism and tissue distribution of histamine; (b) the physiological roles proposed for histamine in normal and pathological states; (c) the chemical classification and pharmacology of antihistamines; (d) the established usefulness of antihistamines for treating allergic rhinitis, motion sickness and parkinsonism; (e) the possible usefulness of antihistamines in treating dermatoses, cardiac arrhythmias, peptic ulcer, insomnia and snakebite; (f) the lack of effectiveness of antihistamines in cases of headache, bronchial asthma, anaphylaxis and the common cold; and (g) adverse effects, drug interactions, toxic overdose and abuse of antihistamines.

KEY WORDS: Antihistamines, histamine

HISTAMINE

Endogenous histamine (β -imidazolyethylamine) originates from the decarboxylation of L-histidine, an event catalyzed by L-histidine decarboxylase, a specific enzyme requiring pyridoxal-5-phosphate as a cofactor.¹ Although tissue histamine is mostly found in basophils or sequestered in the storage granules of mast cells, certain histamine-rich tissues (epidermis, central nervous system (CNS), gastrointestinal mucosa) contain few mast cells. In these latter tissues, the brisk histamine turnover rates may result from the immediate release of newly-formed amine. Most tissues have the ability to catabolize histamine rapidly. In humans there are two major pathways for histamine catabolism: (a) conversion to methylimidazole acetic acid by the sequential actions of histamine-N-methyltransferase and monoamine oxidase; and (b) oxidative deamination by diamine oxidase and subsequent conjugation to form ribosyl imidazole acetic acid.^{2,3}

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A useful classification of histamine receptors, analogous to that already achieved with the catecholamines (alpha and beta receptors) and parasympathomimetic agents (muscarinic and nicotinic receptors), has recently emerged. Currently, histamine receptors are divided into H_1 and H_2 types. The empirical basis for this codification rests upon the differential effects noted in several bioassay systems with either histamine-like agonists or histamine antagonists.^{4,5} As examples, bronchoconstriction and gut contraction are now termed H_1 receptor actions, gastric acid secretion is labelled H_2 receptor activity, and vascular dilation is considered to be a mixture of both.

Histamine exerts its major physiologic effects on smooth muscle and exocrine gland secretion. Histamine produces an impressive drop in systemic blood pressure by decreasing peripheral resistance via a direct dilator action on the smooth musculature of the arterioles, capillaries, and venules. Capillary dilation is accompanied by increased capillary permeability, leading to exudation of fluid. While histamine is a powerful constrictor of the bronchioles, especially in asthmatics, it has little measurable effect on the nonvascular smooth musculature of the bladder and iris. Histamine is also a remarkable secretagogue that evokes a copious output of gastric acid and pepsin. Similar actions on salivary, pancreatic and lacrimal secretions are small and inconsistent.

Because of the varied actions of histamine, it has been suggested that its rate of biosynthesis may be an integral part of homeostatic mechanisms. Indeed, histamine can augment local blood supply and endothelial permeability, and stimulate the pituitary-adrenocortical and reticuloendothelial systems — all of which serve to maintain homeostasis.⁶

Since it is such a potent autacoid, it is not unexpected that histamine has been implicated in the pathogenesis of allergic rhinitis, pain and itching, anaphylaxis, headaches, parkinsonism, bronchial asthma and peptic ulcers.

CLASSES OF ANTIHISTAMINIC AGENTS

Inhibitors of L-histidine decarboxylase (e.g., bromocresine and α -hydrazinohistidine), histamine-N-methyltransferase (e.g., chloroquine) or diamine oxidase (e.g., aminoguanidine) have found

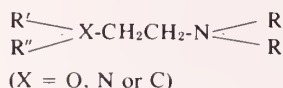
TABLE 1

NONPROPRIETARY NAMES AND REPRESENTATIVE TRADEMARKS
FOR H₁-BLOCKING ANTIHISTAMINES

Class	Nonproprietary Name	Representative Trademark
Ethanalamines	Diphenhydramine	Benadryl
	Dimenhydrinate	Dramamine
	Bromdiphenhydramine	Ambodryl
	Carbinoxamine	Clistin
	Doxylamine	Decapryn
	Orphenadrine	Disipal
	Chlorphenoxamine	Phenoxene
	Phenyltoloxamine	Bristamine
Ethylenediamines	Pyrilamine	Neo-Antergan
	Tripeleennamine	Pyribenzamine
	Antazoline	Vasocor-A
	Methapyrilene	Histadyl
	Chlorothen	Tagathen
	Thenyldiamine	Thenfadil
Alkylamines	Chlorpheniramine	Chlor-Trimeton
	Dexchlorpheniramine	Polaramine
	Pheniramine	Trimeton
	Brompheniramine	Dimetane
	Pyrrobutamine	Pyronil
Piperazines	Chlorcyclizine	Di-Paralene
	Cyclizine	Marezine
	Meclizine	Bonine
	Bucizine	Bucladin-S
	Hydroxyzine	Atarax
Phenothiazines	Promethazine	Phenergan
	Chlorpromazine	Thorazine
	Isothipendyl	Theruhistin
	Trimeprazine	Temaril
	Methdilazine	Tacaryl
Miscellaneous	Phenindamine	Thephorin
	Dimethindene	Forhistal
	Mebhydroline	Incidal
	Cyproheptadine	Periactin

no practical clinical application in any diseases in which histamine has been implicated.

The common structural feature of the classical antihistamines (H₁-receptor blockers) is a substituted ethylamine, a moiety also present in histamine.



This portion of the antihistamine molecule probably competes with histamine for tissue receptor sites, thereby preventing histaminic action. Most antihistamines are known to be competitive antagonists of histamine. They neither combine chemically with histamine to cause its inactivation, nor interfere with histamine release from storage sites.

Antihistamines are classified according to chemical structure (cf. Table 1). Some of the drugs listed in the table and the following groups are no longer commercially available. They were included, nonetheless, for historical reasons, since they will be encountered often in the extensive literature on antihistamines.

Ethanalamines

The drugs in this group are potent histamine antagonists, noted for their sedative and atropine-like

properties. They also appear to produce a low incidence of side effects.⁷ The oldest, most widely recognized members of this group are diphenhydramine and dimenhydrinate. Other agents include bromdiphenhydramine, carbinoxamine, doxylamine, orphenadrine, chlorphenoxamine, and phenyltoloxamine.

Ethylenediamines

These compounds are highly effective antihistamines which produce less sedation than the ethanalamines, but an increased incidence of gastrointestinal side effects.⁷ Two drugs, pyrilamine and tripeleennamine, represent the oldest and best-known antihistamines. Others in the group are antazoline, methapyrilene, chlorothen and thenyldiamine.

Alkylamines

Drugs in this series produce less sedation and more CNS stimulation than the ethanalamines and ethylenediamines. Because of the lower incidence of drowsiness, these compounds have had widespread daytime use. Members of this group include chlorpheniramine, dexchlorpheniramine, pheniramine, brompheniramine and pyrrobutamine.

Piperazines

The antihistamines in this group are best known for their ability to antagonize motion sickness. The oldest piperazine, chlorcyclizine, is no longer available. Cyclizine and meclizine are the best known piperazine antihistamines. Bucizine is less well-known, and hydroxyzine has seen more use as an antianxiety agent than as an antihistamine.

Phenothiazines

Although these drugs have antihistaminic activity and are often used as antihistamines, most are better known for their antipsychotic effects. Representative phenothiazines are promethazine, chlorpromazine, isothipendyl, trimeprazine and methdilazine.

Miscellaneous

Phenindamine, dimethindene, mebhydroline and cyproheptadine do not precisely fit in any of the five classes of antihistaminic drugs described above, although cyproheptadine bears some structural resemblance to the phenothiazines.

Combination Preparations

Many commercial preparations contain antihistamines in combination with other antihistamines or sympathomimetic drugs, anticholinergic agents, antitussives, analgetics or antibiotics. Some combinations may be of value (e.g., a combination of antihistamines to reduce the incidence of certain side effects, like drowsiness, or use of an antihistamine plus a sympathomimetic agent to relieve nasal congestion⁸), but the value of many has not been established. Before using these combinations, consideration should be given as to whether the patient

needs all the ingredients in the compound and whether the dose of each component is appropriate. Disadvantages of using combinations are that (a) the patient often receives drugs which are not indicated or are of no therapeutic benefit in his case; and (b) the amount of each individual drug is not optimal. The potential advantages include reduced cost, increased patient compliance and ease of administration.⁹

PHARMACOLOGY AND THERAPEUTICS

Thirty-four years ago the first clinical use of a relatively nontoxic antihistamine, phenbenzamine (Antergan), was reported.¹⁰ Since then numerous antihistamines have been marketed. Most of the newer drugs, however, do not offer any unique therapeutic advantages over the older compounds.

General Aspects

The rationale for antihistamine therapy derives from the ability of these drugs to antagonize many physiologic actions of histamine, thereby reducing the intensity of histamine-related pathological states. Antihistamines provide only palliative and symptomatic relief and are more effective in preventing the actions of histamine than in reversing those actions once they develop. Clinical differences among various antihistamines result from differences in secondary pharmacologic properties not directly related to histamine antagonism.¹¹

The antihistamines are quite effective in (a) blocking histaminic stimulation of the smooth muscle of large blood vessels, uterus, and gastrointestinal tract; (b) decreasing the extent of the "triple response" by antagonizing the increased capillary permeability and edema formation produced by intradermal histamine injection; and (c) suppressing flare and itch, thus diminishing the pruritis which accompanies allergic reactions or endogenous release of histamine. These drugs also have local anesthetic properties, but this has no established clinical importance.

Pharmacokinetics

Dosage regimens of a number of drugs used in clinical practice have come to be based upon pharmacokinetic principles.¹² Unfortunately, pharmacokinetic data are not available for many of the older, widely used antihistamine preparations. Recent reports have described the pharmacokinetics of various antihistamines,¹³⁻¹⁵ but these data have not yet found their way into the clinical literature. There are, to the best of our knowledge, no extensive summaries of antihistamine pharmacokinetic data available at this time.

While the following general principles, elucidated in a recent review of pharmacokinetics in the aged,¹⁶ have not been proven to apply directly to the antihistamines, they may eventually be shown to pertain to the antihistamines.

(1) The incidence of adverse reactions is higher

in the elderly.

- (2) Barring gastrointestinal pathology, the rate and extent of drug absorption will not be appreciably altered in the elderly.
- (3) Factors such as altered plasma volume, body fat, serum albumin and total body water may cause alterations in plasma drug levels, while decreased renal and extrarenal clearance may slow the excretion of drugs in the elderly.

Clinical Uses

Anaphylaxis. Antihistamines block histaminic bronchoconstriction in man and in the guinea pig¹⁷ (a classic method of assaying for antihistamine effect). However, mechanisms other than histamine release are important in human anaphylaxis. The antihistamines are weak antagonists of bronchospasm induced by antigen-antibody reactions¹⁸ and other bronchoconstrictors, such as the kinins. Because antihistamines are relatively slow to act and do not completely antagonize histamine, they are of limited value in treating human anaphylaxis. The mainstays of therapy in systemic anaphylaxis continue to be epinephrine and steroids.

Peptic ulcer. Antihistaminic effects on the exocrine glands are variable. They block histaminic stimulation of salivary gland secretion but do not affect the increase in gastric acid secretion provoked by histamine. Although pyrilamine, ciproheptadine and chlorpheniramine have been reported to prevent hemorrhagic ulceration in rats given polymyxin B, a histamine-liberator,¹⁹ currently available antihistamines (H₁-receptor blockers) are of little value in treating peptic ulcers. Nevertheless, promising research is being conducted in this area. Two experimental drugs, metiamide and cimetidine, both H₂-receptor antagonists, significantly inhibited gastric acid secretion in men with duodenal ulcers.²⁰⁻²³ Intragastric metiamide caused prompt cessation of bleeding in 10 of 11 patients with erosive gastritis and duodenitis.²⁴ The results are consistent with an important role of gastric acid in the pathogenesis of hemorrhage secondary to stress erosions in the stomach and duodenum.²⁵ Transient agranulocytosis and neutropenia have occurred in patients receiving chronic oral metiamide therapy.^{20,21} These bone marrow depressant effects may be caused by the thiourea moiety of metiamide. Cimetidine, in which a cyanoguanidine residue has replaced the thiourea moiety, reportedly produces no hematopoietic toxicity in animals²⁶ and man.^{22,23,27}

Common cold. The antihistamines are widely used for symptomatic relief of upper respiratory infections caused by viruses. It is well-established that these agents have neither an antiviral effect nor shorten the duration of the common cold.²⁸ A decrease in nasal congestion occurs following therapy with either an antihistamine or a combination of an antihistamine and a sympathomimetic drug. The atropine-like effects of antihistamines may diminish

rhinorrhea in the early phases of a cold, but it is doubtful that they decrease nasal congestion in the later stages.²⁹ If allergic rhinitis is superimposed or if sedation is desired, antihistamines may be useful adjuncts to other symptomatic therapy.

Allergic rhinitis. In 70 to 95 percent of patients, symptoms of allergic rhinitis may be partly relieved by antihistamines.³⁰ These drugs are more effective in relieving symptoms of acute allergic rhinitis than those of chronic conditions, and are of limited value in perennial vasomotor rhinitis. In seasonal hay fever, maximal symptomatic relief is realized during periods when the pollen counts are low. When congestion becomes refractory to treatment, concomitant use of a sympathomimetic agent has improved therapeutic results.³¹ The antihistamines also reduce certain side effects of the sympathomimetic drugs, such as secondary rebound and mucosal irritation. Continual use of intranasal preparations containing antihistamines may lead to severe irritative rhinitis.

Bronchial asthma. Although histamine synthesis and release have long been recognized as early events in the pathogenesis of asthma,³² and chlorpheniramine has been reported to improve pulmonary function in some mild cases of asthma,³³ antihistamines are still considered as relatively ineffective drugs for treating bronchial asthma uncomplicated by allergic rhinitis.³⁴ Also, antihistaminic inhibition of salivary and bronchiolar secretions may aggravate status asthmaticus. Recent studies of the circadian rhythms associated with drug effectiveness³⁵ may help to explain such unresponsiveness to antihistaminic therapy. A chronopharmacologic study in asthmatic subjects revealed a circadian rhythm in bronchial hyperactivity to histamine.³⁶ The time period during which the reactivity was most pronounced coincided with those night hours when asthmatic patients often complain of dyspnea. The antagonism by cyproheptadine of the tissue response to intradermally-injected histamine also varied with the time of day, exactly mirroring the rhythm noted for histamine.³⁷

Cromolyn (Aarane[®], Intal[®]), which is not a true antihistamine, has shown some promise in treating asthma, particularly in children.³⁸ Cromolyn produces no bronchodilation. Its beneficial effect probably results from its ability to inhibit the release of histamine and slow-reacting substance of anaphylaxis (SRS-A) from human lung during allergic responses.³⁹ The benefits of cromolyn are exclusively prophylactic; it is of no use once an asthmatic attack has started. Important disadvantages of cromolyn therapy include its cost and the inconvenience of a daily routine involving multiple doses by the inhalation route.⁴⁰ Xanthine derivatives (e.g., theophylline) remain the prophylactic mainstay for asthma therapy.⁴¹

Motion sickness. The antihistamines have been used extensively in the treatment of motion sick-

ness. Laboratory studies and clinical trials show that diphenhydramine, cyclizine, meclizine and promethazine are of definite therapeutic value.⁴² These drugs are most effective antiemetics when given prophylactically. While there is no substitute for hyoscine (scopolamine, a belladonna alkaloid) for rapidly-acting, short-term protection against exposure to severe motion, antihistamines are the drugs of choice for the prophylaxis of motion sickness during long voyages.

Parkinsonism. In 1947, McGavack et al treated four subjects suffering from parkinsonism with diphenhydramine.⁴³ The improvement noted in three patients was attributed to the therapeutic effects of the antihistamine. Since that report, a variety of antihistamines (viz., chlorphenoxamine, orphenadrine, phenindamine) have been employed with therapeutic effect. The antiparkinsonian effects of antihistamines may relate to their ability to block the cholinergic (muscarinic) receptors in the CNS, based upon the belief that the symptoms of Parkinson's disease are aggravated by a cholinergic imbalance that results from the decrease in striatal dopamine. When efficacious, antihistamines cause fewer peripheral side effects than levodopa.⁴⁴ However, antihistamines offer little benefit for the tremor or sialorrhea of Parkinson's disease. They are most commonly used as adjuncts to levodopa therapy, since they reduce anxiety and insomnia commonly associated with levodopa.⁴⁵ Phenothiazines are contraindicated in patients on levodopa, because they block dopamine receptors and may lead to exacerbation of the movement disorder.

Although (a) antihistamines are helpful in treating parkinsonism and (b) tremorine, a drug used in animals to produce experimental parkinsonism, doubles the histamine levels in the canine corpus striatum,⁴⁶ a role for histamine in the etiology of this disease is presently unsubstantiated.

Modern therapy with levodopa or the combination of levodopa and carbidopa (Sinemet[®]) represents the most rational and efficacious form of drug treatment for parkinsonism.^{47,48}

Children given phenothiazines for the relief of nausea and vomiting have developed serious extrapyramidal reactions^{49,50} which subside soon after the withdrawal of the offending agent. Parenteral injections of diphenhydramine or benztropine (Cogentin[®]) rapidly arrest and usually reverse such symptoms.

Cardiac arrhythmias. At concentrations higher than those usually obtained therapeutically, some antihistamines exhibit antiarrhythmic activity. Antazoline, the most thoroughly studied antihistamine in this regard, has produced favorable results in the management of several types of cardiac arrhythmia. Antazoline suppressed the ectopic beats in premature atrial and ventricular systoles, achieved conversion to sinus rhythm in episodes of paroxysmal atrial and nodal tachycardia and terminated episodes of paroxysmal ventricular tachy-

cardia.⁵¹ This antihistamine proved ineffective, however, in cases of atrial fibrillation and flutter. Antazoline appears to act by depressing the maximal rate of depolarization of the cardiac action potential. The role of antazoline in clinical antiarrhythmic therapy remains to be clearly established.⁵²

Headache. Injected histamine can trigger intense, migraine-like headaches via cerebrovascular dilation. Blood vessels biopsied during migrainous episodes contain fewer mast cells than normal, and the mast cells present tend to be degranulated.⁵³ Such findings have suggested that histamine may be involved in the genesis of migraine. Histamine may also be related to cluster headaches. Indeed, severe cluster headaches accompanied by ipsilateral lacrimation and rhinorrhea have been termed *histaminic cephalalgia*.⁵⁴ These hypotheses are as yet unproven, and it is well-established that antihistamines are ineffective in the treatment of cluster headaches. Although an improvement rate of 46% has been reported in migrainous patients given cyproheptadine,⁵⁵ ergotamine (Ergomar®) still remains the most reliable prophylactic agent against incipient migraine attacks.

Insomnia. Sedation is a prominent side effect of many antihistamines. This has led to their widespread use as sedative-hypnotic agents, especially in the pediatric and geriatric populations.

Most over-the-counter (OTC) sleep medications available in the United States contain methapyrilene (Nytol®, Dormin®) or methapyrilene combined with scopolamine (Sominex®, Sleep-eze®, Quiet World® and Compoz®). These OTC products are most useful in cases of mild insomnia arising from such minor problems as a full bladder, hunger or an uncomfortable bed. They appear to be ineffective in relieving moderate to severe insomnia.⁵⁶ In a trial of hypnotic effect in hospitalized patients, methapyrilene was found to be no different from placebo.⁵⁷ Diphenhydramine was significantly better than placebo in the same study. Hence, it was suggested that diphenhydramine might be a more effective nonprescription sleep preparation. This expectation was recently substantiated in a trial during which children with a variety of sleep disorders were given a diphenhydramine elixir prior to bedtime.⁵⁸

Methaqualone, a nonbarbiturate hypnotic agent,⁵⁹ is marketed in the United Kingdom in combination with diphenhydramine (Mandrax®). Mandrax is a better hypnotic drug than either of its constituents or placebo;⁶⁰⁻⁶² however, it has a considerable potential for abuse and addiction.⁶³ Methaqualone is now regulated under the Comprehensive Drug Abuse Prevention and Control Act of 1970.

Dermatosis. Antihistamines evoke a favorable response in many cases of acute allergy, urticaria and pruritus, but their value in treating the pruritus

associated with various chronic dermatoses is less clear. In recent clinical trials, hydroxyzine proved more effective than (a) diphenhydramine and cyproheptadine in inhibiting histamine-induced pruritus;⁶⁴ and (b) cyproheptadine in relief of pruritus secondary to allergic dermatoses.⁶⁵ Many patients respond to placebo, leading some authors to doubt that the various antihistamines have significantly different antipruritic properties.^{66,67}

Initial studies suggested that antihistamines reduce the pruritus and pyrogenic response during transfusion reactions, but it now appears that their value is limited only to the prevention of allergic transfusion reactions.⁶⁸

Snakebite. Phospholipase A, one of the numerous enzymes found in snake venoms, is a histamine liberator,⁶⁹ thus contributing to the clinical manifestations (shock, edema) of snakebite. It has been reported that a victim of a viper bite responded rapidly to intramuscular injections of chlorpheniramine,⁷⁰ and intravenous administration has been proposed for similar situations.⁷¹ In the absence of a specific pit viper antivenin, antihistamines and steroids have been used with some success.⁷² Notwithstanding, antihistamines are considered to be most beneficial as supportive therapy to control allergic reactions to antivenins.^{73,74} Specific antivenins, when they exist, are the agents of choice.

ADVERSE EFFECTS

The majority of clinically important adverse effects of antihistamines are related to the CNS. However, documentation of other less-well recognized side effects is fragmentary and anecdotal.

Central Nervous System

Sedation, dizziness, tinnitus, incoordination, inability to concentrate, blurred vision, diplopia, fatigue, euphoria, nervousness, insomnia and extrapyramidal reactions have been reported in patients receiving antihistamines.^{7,75} Sedation is the most common side effect; this property has led to the use of antihistamines as sedative-hypnotics, as described in the section on insomnia. Both mental and motor performance may be impaired. Such impairment has been documented during high altitude stress.⁷⁶ Symptoms of CNS stimulation are occasionally seen with therapeutic doses but occur more often with toxic doses, especially in the pediatric age group. This has led to therapeutic errors in emergency rooms where a stimulated child is given an antihistamine as a "safe" sedative when the child is already experiencing antihistamine toxicity.⁷⁷ Following administration of antihistamines, various changes in normal electroencephalograms have been reported, as well as seizures in patients with focal cerebral lesions.^{78,79}

Blepharospasm, pharyngeal dysphagia, nasal regurgitation of food, and dysarthria have been linked to the use of chlorpheniramine, bromphenir-

amine, and phenindamine.⁸⁰ Similarly, oral dyskinesia was reported to occur after the prolonged use of mebhydroline, another nonphenothiazine antihistamine.⁸¹ The symptoms of tardive dyskinesia persist for long periods of time after withdrawal of the drug. Reserpine has been recommended to relieve these symptoms, but, in general, treatment is unsatisfactory.

Autonomic Nervous System

Some antihistamines produce side effects by alpha-adrenergic blockade, as well as atropine-like side effects by antagonizing the action of acetylcholine. Voiding difficulties, dysuria, impotence, dryness of the mouth, headaches, and palpitations have been reported. Antihistamines should be given cautiously to patients with narrow angle glaucoma, because these drugs may raise intraocular pressure.

Cardiovascular System

Cardiac arrest following intravenous administration of antihistamines has been reported.^{82,83} Hypotension and hypothermia due to alpha-adrenergic receptor blockade and lowered peripheral resistance may be seen following large doses of antihistamines, especially the phenothiazines.

Blood Dyscrasia

Several cases of agranulocytosis have been reported in patients on chronic tripeleonnamine therapy.^{84,85}

Gastrointestinal

Gastrointestinal symptoms, including loss of appetite, nausea, vomiting, and abdominal distress accompanied by diarrhea or constipation have been reported.⁸⁶ The phenothiazines can occasionally cause cholestatic jaundice.

Teratogenicity

Although morphological abnormalities have been observed in animals given large doses of antihistamines early in gestation,^{87,88} definitive proof of teratogenicity in humans has not been established. Nonetheless, in the United States, the FDA has recommended that manufacturers issue warnings in their package inserts that antihistamines are contraindicated during pregnancy.⁸⁹

Allergy Formation

Allergic reactions to the antihistamines are known. Allergy can occur following oral therapy, but is far more common following topical administration. For this reason, the use of topical preparations containing antihistamines (e.g., calamine and diphenhydramine) is discouraged.

DRUG INTERACTIONS

Because of an increased risk of atropine-like side effects, the ethanolamine antihistamines

should be avoided in elderly patients being treated with tricyclic antidepressants.⁹⁰ Patients should be cautioned against taking alcoholic beverages or barbiturates while using antihistamines, since the CNS depressant action of these drugs is additive.⁹¹ Promethazine treatment should be terminated prior to intravenous administration of thiobarbiturates, because promethazine may decrease the anesthetic effectiveness of the barbiturate.⁹²

A study of the metabolism of chlorcyclizine and diphenhydramine in dogs indicated that these antihistamines may stimulate their own metabolism and the metabolism of other drugs by inducing hepatic enzymes.⁹³ However, in human studies, in which plasma antipyrine and phenylbutazone half-lives and urinary output of 6 β -hydroxycortisol were used as indices of drug-metabolizing capacity, diphenhydramine did not induce liver microsomal enzyme activity.⁹⁴

TOXIC OVERDOSES

Despite a relatively wide margin of safety, the widespread availability of antihistamines has resulted in frequent toxic overdoses.^{75,95} The H₁-receptor blockers produce a mixture of excitatory and sedative manifestations. The excitatory symptoms often predominate in the pediatric population. The findings of fixed, dilated pupils, flushing, and fever, especially in the pediatric group, often mimic the classic findings of atropine poisoning ("dry as a bone, red as a beet, and mad as a hatter"). Adults frequently demonstrate findings which spontaneously progress from drowsiness (sedation) into excitement and convulsions, followed by postictal depression. Close monitoring is mandatory during the toxic period. When a potentially lethal dosage of antihistamine has been ingested, the patient tends to lapse into a progressively deepening coma. Death usually results from cardiorespiratory collapse.

There is no good specific therapy for antihistamine overdose. The phenothiazines are not dialyzable;⁹⁶ diphenhydramine overdose has been treated by exchange transfusion,⁹⁷ and this drug was shown to be partially dialyzable.^{98,99} In most situations, correcting fluid and electrolyte imbalance and other supportive therapy, utilized as clinically indicated, is sufficient to assure survival. Physostigmine is the treatment of choice for certain types of poisoning (atropine, belladonna alkaloids, tricyclic antidepressants) and may be of clinical use as an antidote for antihistamine intoxication.¹⁰⁰

ABUSE

At doses approaching toxic amounts, antihistamines are hallucinogenic. Although less popular than barbiturates and amphetamines, antihistamines have been used to produce deliberate intoxication. Two young men, each of whom ingested 800 mg of dimenhydrinate, reported experiencing similar visual hallucinations (colored lights) and

formication.¹⁰¹ A young girl had an acute schizophrenic reaction following ingestion of 500 mg of diphenhydramine.¹⁰² She returned to a normal mental state within 48 hours after taking the antihistamine.

When abuse of methaqualone was rising in popularity, British investigators documented abuse of the combination product, Mandrax.^{103,104} Because the clinical manifestations of Mandrax poisoning closely paralleled those produced by methaqualone itself, it was thought that diphenhydramine did not contribute significantly to Mandrax toxicity.¹⁰⁴

In the United States a mixture of paregoric concentrate and tripeleminamine tablets, referred to as "Blue Velvet," has been abused by the intravenous route.¹⁰⁵ "Blue Velvet" causes an immediate euphoria which lasts for several hours, but it is highly sclerosing, often forcing the intravenous abuser to eventually utilize jugular vein injections.

COMMENT

Antihistamines are valuable drugs for treating a number of conditions and diseases (e.g., allergic rhinitis, motion sickness and parkinsonism), but proof of efficacy has not been established in such areas as the treatment of cardiac arrhythmias, peptic ulcers, insomnia, and headache. No single antihistamine is therapeutically unique. The best results will be obtained by selecting a limited number of these drugs and learning their pharmacological actions. Because responses to antihistamines may vary, titration of each patient's dose is recommended.

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Maine Blue Cross and Blue Shield News

PHYSICIANS' OPINION SURVEY: PART II

In an effort to better define physicians' attitudes towards Maine Blue Shield, a group from the Research and Provider Affairs Department developed a "Physicians' Opinion Survey" during March of 1976. The survey was distributed at county medical society meetings during the months of April and May. It was also distributed to the following committees: Osteopathic State Peer Review, Osteopathic Insurance, Maine Medical Association Committee on Health Care Financing, and the Maine Medical Association Advisory Committee on Health Care Planning. At the same time, a letter was distributed to all physicians informing them that we had drafted a survey. A few physicians requested and received a copy of the survey as a result of this letter.

Of the 270 surveys distributed, 80, or 30%, were returned. The following is the second half of a rough tabulation of the survey results.

Of the written communications which reach physicians from Blue Shield, the article in the *Journal of the Maine Medical Association* received an adequate to good rating from 48% of the respondents (43% do not read or did not respond), the *Healthcare Update* newsletter received an adequate to good rating from 64% of the respondents (28% do not read or did not respond), and other Blue Shield mailings received an adequate to good rating from 80% (16% do not read or did not respond).

The Maine Blue Shield toll-free number was seen as helpful by 41%, 20% did not know it existed, 21% lived in the Portland area so the toll-free aspect would make no difference, and others did not respond or do not use the line for other reasons.

The next question asked physicians to rate third-party payors in Maine on six different aspects: fees, ease of administration, etc. In every case, Maine Blue Shield was rated highest in the good to adequate categories.

Eighty percent of the respondents felt that they understood Blue Shield Programs adequately to well, while 71% felt that their patients did *not* understand Blue Shield programs adequately.

Forty-one percent of the respondents agreed with a past decision to offer Blue Shield outpatient lab benefits as a rider only because of financial situations, while 30% wanted a rider for both Blue Shield and Blue Cross.

The next question requested that respondents rate three alternatives for expansion of Blue Shield benefits or offer their own suggestion for expansion of benefits. The three alternatives were office lab, emergency medical treatment, and more cardiac diagnostic procedures. Emergency medical was the first or second choice of 73% of the respondents while office lab was chosen 1st or 2nd by 54% of the respondents.

Blue Shield currently pays non-participating physicians 80% of the contract's amount for a service. Forty percent of the respondents agreed with this level, and 26% felt non-participating physicians should receive 100%. Sixteen percent felt that non-participating physicians should receive less than 80%.

Sixty-four percent felt favorably toward reimbursement for a second opinion for elective surgery, 13% were neutral, and 17% against.

Some Plans require Utilization Review of Blue Shield claims, and 44% of the respondents felt favorably about this practice, 24% were neutral, and 26% against.

Of the Plans requiring utilization review, some are considering the use of PSRO as a final review mechanism. Sixty-one percent liked this idea, 13% were neutral, and 21% did not like it.

When asked to react to the idea of a formal negotiation between Blue Shield and the medical and osteopathic societies on such issues as service benefit income limits and UCR levels, 74% were favorable, 6% neutral, and 13% unfavorable.

County Society Notes

Report from York County Medical Society

Nursing Perspectives Related to the Concept of Depression – Another Venture in Education

MELVIN BACON, M.D.*

As is well known, I have been involved in professional and non-professional education for years in York County. This will become evident from an article in Education by myself which appeared in the September 1976 issue of *The Journal of the Maine Medical Association*. Therefore it will be unnecessary to say anymore about them.

The idea had occurred to me that it would be worthwhile to set up a Workshop on Psychiatry. With this in mind, I contacted Mary Ann Rost, R.N., M.S.,** and Anna Bowe, R.N., B.S.,*** and between the three of us a Workshop on Nursing Perspectives Related To The Concept of Depression was developed and was held on April 5, 1976, at the Hilltop House, Nason College, Springvale, Maine. Because of the success of this program, it was deemed of interest to present this paper.

This Workshop was sponsored jointly by the Bureau of Continuing Education for Nursing, University of Maine at Portland-Gorham, the H.D. Goodall Hospital, the Sanford-Springvale Community Health Association, and the York County Public Health Nursing Association. It was primarily for R.N.'s and L.P.N.'s practicing in the community, hospitals, nursing homes, boarding homes and industry and also for nursing students. All those from these categories from all over Maine were invited to attend.

This course was approved for 0.6 C.E.U.'s by the Maine State Nurses Association and had the approval of the Maine Medical Association and the York County Medical Society.

The purpose was to provide the opportunity for workshop participants to explore theoretical relationship between anxiety and depression in selected life phases.

The objectives were that at the completion of this one-day workshop, participants would be able to:

1. Identify the theoretical relationship of anxiety and depression as seen in the client and self.
2. Relate above concepts to the care of new mothers and newborns as well as to the elderly.
3. Describe the nurse's role in psycho-pharmacology.
4. Describe applicable resources provided by the York County Counseling Service.

The program was as follows:

- 8:00- 9:00 A.M. Registration
- 9:00- 9:05 A.M. Welcome — Carl Richards, M.D., President, Medical Staff, H.D. Goodall Hospital, Sanford, Maine
- Moderator — Melvin Bacon, M.D., Workshop Director, Director of Education, H.D. Goodall Hospital, Sanford, Maine
- 9:05-10:00 A.M. "Relationship Between Anxiety and Depression" — Kathleen MacPherson, R.N., B.S., University of Maine School of Nursing, Portland, Maine
- 10:00-10:15 A.M. Coffee
- 10:15-11:15 A.M. "How to Deal With Anxiety and Ensuing Depression"
- In self
 - With clients in repetitive situations

*Workshop Director, Director of Education, Goodall Hospital, Sanford, Maine.

**Director, Bureau of Continuing Education for Nursing, University of Maine, Portland, Maine.

***Program Director, Mental Health Social Services, York County Counseling Services, Inc., Biddeford, Maine.

This workshop was made possible in part by a grant from the Merck Sharp & Dohme Postgraduate Program.

such as child abuse, abortion, suicide.
Kathleen MacPherson, R.N., B.S.

11:15-12:15 P.M. "Anxiety and Depression in the New Mother"

- Expectations
 - The deformed or retarded child.
- Geraldine Tukey, R.N., M.S., University of Maine School of Nursing, Portland, Maine

12:15- 1:15 P.M. Lunch

Afternoon
Moderator

— Anna Bowe, R.N., B.S., Program Director, Mental Health Social Services, York County Counseling Services, Inc., Biddeford, Maine

1:15- 1:45 P.M. "Nurses Role in Psycho-pharmacology"

- Open discussion, handout material
- Kathleen MacPherson, R.N., B.S.

1:45- 3:00 P.M. "Problems in the Elderly"

- Theories of Behavior
 - Support Systems
 - Nurses' Anxieties
- Kathleen MacPherson, R.N., B.S.
Geraldine Tukey, R.N., M.S.

3:00- 4:00 P.M. Resources of York County Counseling Services, Inc., PANEL

- The Partial Hospital
- Virginia Sabib, R.N., M.S.
- After Care
- Joseph Rubin, M.D.
- Children's Services
- Sebastian Milardo, Ph.D.

4:00- 4:30 P.M. Open Discussion, Evaluation

Closing Remarks

Mary Ann Rost, R.N., M.S., Director, Bureau of Continuing Education for Nursing, University of Maine, Portland, Maine

Newspapers were contacted and asked to publicize this endeavor. These included the Portland Press Herald, who were asked to have this information inserted in their newspapers all over Maine, the York County Coast Star, the Biddeford-Saco Journal and the Sanford Tribune. Radio stations WIDE, Biddeford and WSME, Sanford were also requested to announce this. In addition, motel reservations were made available by writing or phoning:

1. Allen's Motel, Main Street, Sanford, Maine 04073
Telephone: 324-2160

2. Bar-H-Motel, South Sanford, Maine 04073
Telephone: 324-4662

Each hospital in the State was sent a program. Participants were instructed to bring their own lunch or they could eat in the Nason College cafeteria.

We were exceedingly pleased with the attendance which numbered approximately 150. Each registrant was requested to complete a simple questionnaire and the remarks were most interesting and revealing.

At the end of the meeting, a show of hands was asked concerning a Workshop on Neurology and the response was overwhelming in favor. I might add at this time that such a program is slated for October 18, 1976.

This paper presents a resumé of the Workshop on Psychiatry for the nurses of Maine. It should serve as a guide for future programs of this nature.

SUMMARY

In conclusion, I want to thank the two nurses, Mary Ann Rost, R.N., M.S., and Anna Bowe, R.N., B.S., with whose help this workshop became a reality and to Mr. George Bently, Director of Administrative Services, Nason College, Springvale, Maine.

who made their facilities available to us for this workshop as well as many others over the years. May I also express my appreciation to all the other participants who made their services available to us. They did a magnificent job.

York

The May meeting of the York County Medical Society was held on May 12, 1976 at the Webber Hospital, Biddeford, Maine. The program was as follows: Social Hour from 6:30 p.m. to 7:30 p.m., with the dinner, speaker and meeting to follow. This meeting was set up through the combined efforts of your president and secretary.

Following a most delicious dinner, Dr. Owen O. Dow, our President, introduced Thomas W. Cathcart and Laura Franciosa of the Maine Blue Cross and Blue Shield of Portland, Maine. Their subject was "Physicians Look at Blue Shield." They gave a most interesting presentation which evoked considerable comment and discussion. This discussion actually became heated at times. Amongst the issues presented was the usual and customary fees charged by physicians and current billing by hospitals. It was also of interest to note from their talk that many subscribers of Blue Cross and Blue Shield do not understand or even read their contracts and that there is a definite need for patient education. Major medical coverage was another item that was brought up. Also mentioned was the increase in hospital costs. A short questionnaire was presented to each physician in attendance to complete to ascertain their views to assist Blue Cross and Blue Shield in future decisions and discussions. Another item of importance brought up was the Statewide disparity of fees charged by physicians and the need for a definite adjustment. One final item that was also mentioned was a question of reimbursement of laboratory fees done in the office. All in all, it was considered an interesting and worthwhile presentation.

Following the talk, our president thanked both speakers and then opened the business meeting. In the interest of time, the minutes of the last meeting were dispensed with. He briefly mentioned the talk given by Dr. McAfee at the March meeting at which he discussed what the State and National Societies are worth to you and I. At this point, Dr. Dow stated there was no old business to be brought up. Amongst the pieces of new business to be brought up was the appointment of several new committees which was deferred. In addition, he asked for approval of the York County Medical Society for a "Workshop on Neurology for the Nurses of Maine" to be held at Nasson College, Springvale, Maine on October 18, 1976. This has already been approved by the Maine Medical Association.

Dr. Dow announced that the next meeting of the York County Medical Society will be held at the York Hospital, York Village, Maine on Wednesday, October 13, 1976 and he would welcome any suggestions as to topics now and in the future.

He also added that since the two excellent turnouts in response to his poignant letter had convinced him as to the Society's vitality, he would see to it to keep the group stimulated and interested.

The next announcement concerned the 123rd Annual Meeting of the Maine Medical Association to be held at the Treadway-Samoset Resort, Rockport, Maine on Saturday-Tuesday, June 5th-8th.

Dr. Carl Richards attended the Interim Meeting of the House of Delegates at the Eastern Maine Medical Center in Bangor, Maine on April 3rd and made comments on it. Others attending were Drs. Bacon, Buell and Ficker (member of the Executive Committee). He discussed the current situation concerning the State and county dues that our president was upset over. The budget for 1977 was also brought up and this included The Journal and the appointment of an Assistant Director and the lobbyist. A slate of new nominations was presented.

There were five resolutions presented. Our society voted in favor of two, against two, and took no stand on another.

Another item discussed was the "Flu Vaccination Program."

All these matters will again be brought up at the House of Delegates in June.

Correspondence was received from the American Medical Association regarding Blood Pressure Screening during the

month of May. As usual, this letter was so late in arriving that there just wasn't enough time to prepare for it.

The need for more frequent county meetings was a constant theme throughout the meeting. Dr. Ross mentioned the paucity of physicians from York County attending Annual Meetings of the Maine Medical Association when held in our own backyard; namely, in Kennebunkport.

Dr. Michael J. Festino then brought up the problem of Malpractice and this was discussed at length. Dr. Richards again reviewed at this meeting as he has done at a previous meeting what was going on Statewide, mentioning the number of meetings that were conducted all over the State. He reiterated the need for reading the Portland Press Herald in order to keep abreast of all current legislature going on in Maine. It was also voted that a special meeting on "Malpractice" be held in September 1976; the program to be set up by your President, Dr. Dow. The door was also left open for future additional meetings.

There were 23 physicians and 5 guests who attended which was considered to be a fruitful meeting replete with discussion.

The meeting was then adjourned.

MELVIN BACON, M.D., *Secretary*

Penobscot

The monthly meeting of the Penobscot County Medical Society was held on April 20, 1976 at the Red Lion Restaurant, Bangor, Maine.

The meeting was opened by the President, Dr. Thornton W. Merriam, Jr. and the minutes were read and approved.

Under old business, the fee schedule agreement reached by the Maine Medical Association with the Veterans Administration was once again discussed. Dr. Merriam presented the background history of this agreement and pointed out how the Finance Committee of the Maine Medical Association arrived at this agreement in the past. Dr. Lewis E. Phillips then introduced the resolution for adoption of this County Society to be forwarded to the Maine Medical Association for inclusion at its annual meeting in June 1976. This resolution requested that the

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Maine Medical Association terminate for its members any agreement or contract which it may have with the Veterans Administration for payment of fees. After appropriate discussion, this resolution was approved by the membership. It will be forwarded to the Maine Medical Association for consideration at the annual meeting.

Dr. Merriam appointed the nominating committee for presentation of its slate of officers for the coming year at the annual meeting of the County Society in May 1976. The nominating committee appointed consists of Drs. Sensenig, Andrews, Watt and Houlihan.

Following the business portion of the meeting, the scientific portion was then begun. This consisted of a presentation by Drs. Richard Barron and Harold Rhineland and Mr. Philip Judd

regarding the use of physician's assistants. Mr. Judd represented Medical Care Development, Inc. and presented a slide presentation on the use of the physician's assistants. This described the definition of the physician's assistants and how he can be utilized by the physician in his daily practice. Dr. Rhineland described the function of the physician's assistant at the New England Medical Center Hospital in Boston, Massachusetts and demonstrated how the physician's assistant is a major part of their surgical program. Dr. Barron related his own personal experience with the physician's assistants in both his office and surgical practice. Following these presentations, numerous questions and answers followed.

As there was no further business, the meeting was adjourned.

PHILIP G. HUNTER, M.D., *Secretary*

Letters to the Editor

To the Editor:

Nosology is the study of causes of death and the assignment of a *single cause* from multiple causes often reported on a record. You, the Doctor, give the information from which all State, National and International Statistics are compiled.

A cause of death is the morbid condition of disease process, abnormality, injury, or poisoning leading directly or indirectly to death. The underlying cause of death is the disease or injury which initiated the train of morbid events leading directly or indirectly to death or the circumstances of the accident or violence which produced the fatal injury. A death often results from the combined effect of two or more conditions. The conditions may be completely unrelated, arising to each other, that is, one cause may lead to another which in turn leads to a third cause.

If a Doctor writes a death record with the immediate cause of death on line (a) and antecedent conditions on lines (b) and (c) which *gave rise* to the cause reported on line (a) with ONE cause to a line, we have a perfect record.

The problems arise for the Nosologist when the perfect sequence is not on the record in its proper order.

The chief working tools of a Nosologist are two volumes of the "International Classification of Diseases," — several manuals and eleven rules set up by the World Health Organization Nomenclature Regulations and two medical dictionaries. The W.H.O. (World Health Organization) regulations require that the coding of causes of death follow their rules for selecting the underlying cause of death so all States' statistics show the same codes on selected diseases.

The chief complaint of an Nosologist is that the doctors use descriptive terms instead of the answers to What? How long? and in the case of external causes Where? When? and How? did the death occur. External causes get the worst of reporting. It is common to have a record of nothing more illuminating than "Fractured Skull" on it, leaving to the imagination whether there had been a homicide or something taken with the afternoon tea! For supplemental information, the Nosologist clips three daily newspapers for such cases whereby she may learn that the deceased was in an automobile accident or fell from a roof at his home on such a day, in such a city, all of which must be typed up and added to the back of the death record for the reports going to National Center for Statistics in North Carolina. This is not the perfect way to find the needed information. Many accidents do not get reported correctly in newspapers, some are not reported at all. Vagueness derives from such terms as "failure," "decompensation," "natural causes" and the like which are by no means the CAUSES of death but effects of something often unnamed. The medical man should not forget that he is first of all a scientist. There are thousands of commonly used words that we can cite, anoxia, ascites, asthenia, cachexia, collapse, coma, debility, etc. that tells us only the person died. These causes must be assigned to "Ill-defined" categories. Cardiac disease and cardiac failure are insufficient and something to ask a doctor about through a query. Occasionally, on receipt of a query, it is disclosed that the cause of death is as elemental as cancer or T.B. Such surprises bring with them feelings of frustration to the Nosologist coding the record. In the case of a Post Operative Myocardial Infarction, the condition necessitating the operation is the information

needed for statistics. For unaccountable reasons, puerperal deaths come to be reported with no suggestions of a pregnancy or even fail to mention a childbirth.

When a death record contains all of the diseases the doctor attended the deceased for connected by "and," "probably," "secondary to" etc., we are forced to apply rules to determine the underlying cause. This may result in selecting something you did not feel was the direct underlying cause of death. Rules state that it is *highly improbable* that diabetes, hemophilia, influenza, cancer are "due to" any other disease. A non-inflammatory disease of the central nervous system, except cerebral embolism, cannot be "due to" endocarditis or to a disease of the digestive system. Another problem arises when a disease reported on line (a) is "due to" line (b) with a duration date that is *longer* than the disease on (b).

Every hour of the working day, good people and better machines work rapidly to report as intelligently as possible two chief facts of life, namely birth and deaths. Of birth, the fact alone is essential, but of death, the usefulness to practitioner and researcher is limited only by the soundness of reporting by the physicians. Please remember it isn't the plumber or the electrician for whom this work is being done. It is for your advantage in the end. Please do not be too put out if you receive a query sheet from a State Nosologist. We need the answer in order to report to the State and National Statisticians what diseases are taking lives that can be saved in the future if more studies are carried out soon. Infantile Paralysis — Cancer etc. show what determined study can accomplish.

You can all help make Maine's statistics the best in the Nation, and your paper work less, if good reporting is done on all death records. Let's eliminate such reporting as "Had never been fatally ill before" — "Died suddenly" — "Nothing serious" — "Died in bed alone"!

MARIAN B. PERKINS
Nosologist, Vital Records
Maine Department of Human Services
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Experience With 100 Patients Hospitalized for Incarcerated Groin Hernia

WINTHROP S. MACLAUGHLIN, JR., M.D.,* IRVING L. KRON, M.D.** and

GEORGE F. SAGER, M.D., F.A.C.S.†

An incarcerated hernia presenting above or below the inguinal ligament may represent a surgical emergency in that it may progress to strangulation with infarction of a viscus. Strangulation may be partial with only pressure on the vessels of the incarcerated viscus or may be complete with congestion, edema and gangrene of the contents of the hernia sac. Since an incarcerated inguinal hernia with viable contents cannot be differentiated from one with non-viable contents on clinical grounds alone,¹ aggressive surgical management is indicated.

It is estimated that the complication rate following repair of groin hernias approaches 10 percent.² In 1962, Marsden reported a mortality rate of 0.5% in a review of 2254 cases of inguinal hernioplasty.³ In 1963, Rydell noted that of 1162 patients undergoing inguinal and femoral hernioplasty, 6% of the children and 9.3% of the adults were hospitalized for irreducible hernias.⁴ Considering the high incidence of hernias in the general population and the paucity of recent literature concerning the results of emergency hospitalization for the complications of incarceration, the following study was undertaken.

METHOD OF STUDY

The hospital records of 100 consecutive patients admitted to or discharged from the Maine Medical Center from March 1968 to January 1976, in whom an anatomical location of the incarcerated hernia

was determined were included in this study. Two patients with non-emergency, chronically incarcerated hernias who were not subjected to operation were excluded from this study. For purposes of analysis, the patients were subdivided into three groups according to age and the following factors were studied: type of hernia, sex of the patient, reducibility of the hernia, nature of the hernia (emergent or non-emergent), contents and viability of the hernia sac, morbidity, mortality and length of hospitalization.

RESULTS

The pediatric group consisted of 33 patients who ranged in age from two weeks to 6½ years with the average age being 2.7 years. This group consisted of 19 males and 14 females, all of whom underwent operation. All incarcerated hernias were of the inguinal variety with 21 being right indirect inguinal hernias and 12 being left indirect inguinal hernias. Attempts at reduction were made in 19 patients and were successful in only 6. Spontaneous reduction of the incarcerated hernias occurred preoperatively in 3 patients. In 10 patients, the attempt at reduction preoperatively was either not made or not stated in the chart. Twenty-six patients were judged to have emergent incarcerated hernias while 8 were non-emergent. The contents of the incarcerated sac could be ascertained in 12 cases and these are summarized in Table 1. None of the incarcerated hernias resulted in strangulation. Two complications (6%) occurred in this group and each was of a minor degree (Table 2). The length of hospitalization ranged from 1 to 6 days with the average stay being 2.6 days.

The middle age group numbered 22 patients with

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TABLE 1

	SAC CONTENTS (Inguinal and Femoral Hernias)		
	<i>Pediatric</i>	<i>Middle Age</i>	<i>Elderly</i>
Appendix	1	0	1 (Acutely inflamed)
Bowel — Small	3	5 (2 gangrenous)	14 (2 gangrenous, one of which was a Richters hernia)
Meckel's Diverticulum	1	0	0
Urinary Bladder			
Diverticulum	0	0	1 (gangrenous)
Tube and Ovary	6	0	0
Omentum	1	9 (3 gangrenous)	8 (1 with metastatic undifferentiated carcinoma)
Sigmoid	0	1	4 (1 with hemorrhagic fluid)
Appendix Epiploica			
of Sigmoid	0	1	0
Cecum	0	1	2

ages ranging from 20 to 58 years, the average age being 44.3 years. All patients in this group were males and all were subjected to operation. Attempts at reduction numbered 11 with only 3 being successful. There was one spontaneous hernia reduction and in 10 patients, reduction was not attempted or, if attempted, was not stated in the table. The incarcerated hernias consisted of 11 right inguinal hernias, 10 left inguinal hernias, and one femoral hernia. Sixteen of 22 patients were considered to have emergent incarcerated hernias and 9 patients had strangulated hernias. Six of the sixteen indirect hernias were strangulated and contained omentum in three cases, sigmoid bowel in one case, small bowel in one case and appendix epiploica in one case. Two of the right and three of the left incarcerated inguinal hernias were direct hernias and of the five incarcerated direct hernias, two were recurrent. Two of the direct hernias were strangulated and contained omentum. The incarcerated femoral hernia contained infarcted small bowel. The most common content of the incarcerated hernia sac was omentum (See Table 1). The complication rate for this group had increased to 31.8%. The length of hospitalization ranged from two to 19 days with the average hospitalization being 7.5 days.

Those included in the elderly group numbered 45 patients who ranged in age from 60 to 90 years with the average age being 77 years. Forty of the patients were male and five were female. Forty-four of the patients were operated on and one incarcerated hernia was diagnosed at post-mortem examination. Preoperative reduction was attempted in 16 cases and only successful in 6 patients. One patient had spontaneous reduction of the hernia while in the hospital. Reduction was not attempted, or if attempted, was not stated in the record in 28 patients. Forty of the forty-five cases were judged to be emergent and 10 cases were considered to be strangulated. Nineteen right inguinal hernias, 23 left inguinal hernias and three femoral hernias were included in this group. The contents of the sac could be ascertained in 30 cases and this is summarized in Table 1. Two of the right and three of the left inguinal hernias were direct. Two of the direct in-

TABLE 2

	COMPLICATIONS		
	<i>Pedi- atric</i>	<i>Middle Age</i>	<i>Elderly</i>
Edematous Testicle or Scrotum	1	2	5
Vomiting	1	0	0
Urinary Tract Infection	0	2	4
Sepsis, Recurrent Hernia	0	1	0
Atelectasis	0	1	1
Wound Infection	0	1	2
Wound Hematoma	0	0	1
Small Bowel Obstruction	0	0	1
Arrhythmia	0	0	1
Rectal Bleeding	0	0	2 (1 patient had divertic- ulosis)
Acute Myocardial Infarction	0	0	1 (with uri- nary tract infection)
Urinary Retention	0	0	2
Deaths	0	0	3

guinal hernias were strangulated and contained strangulated bowel. None of the three incarcerated femoral hernias were strangulated. Of the 37 indirect incarcerated hernias, eight were strangulated and contained omentum in two cases, bowel in five cases and a ruptured urinary bladder diverticulum in one case. There were 20 complications and three deaths in this group for a morbidity rate of 47.6% and a mortality rate of 6.6% (See Table 2). The deaths included a 77-year-old male who had a cardiac arrest and succumbed two hours postoperatively after a repair of an incarcerated indirect left inguinal hernia containing viable bowel; a 63-year-old male who succumbed from small bowel obstruction with aspiration 30 days after repair of an incarcerated indirect right inguinal hernia containing omentum with undifferentiated carcinoma; and a 70-year-old male who died 2½ hours after being admitted to the hospital for gram negative septicemia from small bowel infarction in an incarcerated indirect right inguinal hernia. Three of the patients in the group developed incarcerated hernias while in the hospital. Two of the three were being treated for unrelated conditions and one developed an incarcerated left femoral hernia while being treated for an

incarcerated indirect right inguinal hernia. The length of hospitalization ranged from one to 30 days with the average stay being 10.5 days.

DISCUSSION

Inguinal hernias in childhood appear about 10 times more frequently in males and almost all are indirect inguinal hernias. Despite the greater incidence of hernias in males⁵ than in females, it is interesting to note that 42% of the incarcerated hernias in the pediatric group occurred in females. As has been previously reported and confirmed here, the hernias occurred more frequently on the right and the presence of non-viable viscera in the hernia sac is unusual. No morbidity resulted from the attempts at reduction. The postoperative complications were minimal.

It has been stated that the direct inguinal hernia usually has a broad base and is an infrequent cause of incarceration.⁶ Therefore, it is surprising to find that 23% of the patients in the middle age group and 11.1% of the patients in the elderly group had incarcerated direct hernias. It was also noteworthy that four of the 10 incarcerated direct inguinal hernias were strangulated. Only one of the strangulated direct hernias was a recurrent hernia and as such may have had a narrow neck to its sac. Of the 19 strangulated hernias in the two older age groups, 14 were indirect, four were direct and one was a femoral hernia. Again, there were no complications related to attempted preoperative reduction of the hernia in the two older age groups. As would be expected, the morbidity and mortality rates increased sharply for the middle age and elderly groups undergoing operation for incarcerated hernias. The complication rate ranged from 31.8% in the middle age group to 47.6% in the elderly group with a 6.6% mortality rate in the latter group. This mortality rate contrasts with a mortality rate of 2% for those over 60 years of age undergoing elective inguinal herniorrhaphy.⁷

CONCLUSIONS

The results of eight years' experience with 100 incarcerated hernias are presented. Without subdividing the patients into groups by age, the most frequent incarcerated hernia was the indirect inguinal hernia (86%), followed by the direct inguinal hernia (10%), and lastly by the femoral hernia (4%). Considering the hernias by types, strangulation occurred most frequently in the direct inguinal hernia (40%), followed by the femoral hernia (25%), and occurred least frequently in the indirect inguinal hernia (16%). Though direct hernias incarcerate infrequently, the high percentage of strangulation reflects the serious potential of these particular hernias when they do incarcerate. As would be expected, the morbidity and mortality were greatest in the oldest age group, while the pediatric group tolerated the surgery extremely well. Early diagnosis and aggressive management of hernias is encouraged.

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Dr. MacLaughlin, 16 Sweet Fern Rd., Cape Elizabeth, Maine 04107

Dr. Kron, Maine Medical Center, Portland, Maine 04102

Dr. Sager, 7 Bramhall St., Portland, Maine 04102

Fall Meeting of the M.M.A. House of Delegates

Sunday, December 12, 1976

Mid-Maine Medical Center (Thayer Unit), Waterville, Maine

12:30 P.M. — Registration; 1:00 P.M. — Lunch; 2:00 P.M. — Meeting

10:00 A.M. — Meeting of the Executive Committee

Infectious Threats Hide in New Facilities Too

FRANK W. KIBBE, M.D.

"There is an absence here that thus offends the CAUSE of equal health to all."

One meets at almost every turn of the present hospital life the call by administration and by hospital accreditation for written "policies and procedures." Somehow by "a priori" reasoning this protects the patient whether or not such procedures are, in fact, in practice; for often such bodies negate the importance of such written orders by carefully removing the teeth that would make the procedures bite into the problems of reality.

I give you the example of hospital infection control. For three to four months prior to our moving into a new facility at Penobscot Bay Medical Center, I either called or visited: our own executive director, State Health and Welfare facilities, infection control centers, persons versed in environmental bacteriology and other hospitals, in an attempt to obtain the necessary instructions or information regarding the protection of patients and personnel going into a new building with new equipment and new methods of cleaning, etc. (Some directors and trustees might seem ill at ease that such a question should arise from a medical staff member.) Neither persons nor books helped at all. Lacking such help via either written or spoken word, we undertook to evaluate the situation both architecturally and bacteriologically.

Construction-wise two major sources of contamination were found:

1. Dry wall to metal construction allowed uncleanable cracks, from which circulating air could continuously spread foamites and bacteria throughout the adjacent areas. Such construction in patients' rooms, administrative offices, waiting rooms, etc. may be permissible though cleaning of such cracks is quite impossible, but in Operating Rooms, Delivery Rooms, Sterile Supply, Pharmacy preparation rooms and Nursery, this seems completely inexcusable. The factor of positive pressure circulation does *not* reduce the activity flow of air and monitoring has shown us repeatedly that fall-out plates will double colony counts under the impact of increased activity and increased air movements. (We noted this first in the Operating Rooms where orthopedic procedures requiring hip nailing with the taking of x-rays and thus the presence of many moving bodies more than doubled our period counts over regular O.R. procedures such as gallbladder removal or even dirty cases such as bowel surgery.)

2. Another, though potentially less lethal feature, was the ever-present protruding door or window frame. Here, the ledge may be cleaned of its ac-

cumulated dust and debris with the enclosed lethal load of bacteria, fungi, etc., but since we are so constantly reminded of the escalating costs of hospitals, one sees such cleanings as either being too expensive or being neglected. Often administration, under such circumstances, insists on written protocol but then denies the necessity of monitoring the areas involved. One sees it bowing to the holiness of the written word and the avoiding ways to learn of deficiencies in the "system". I quote from the AHA's Committee of Infections within hospitals stating: "The Committee . . . finds no evidence that routine environmental sampling is necessary to maintain good practices in the hospital." This should be framed as a religious doctrine of great faith in the human and his methods.

Fortunately, some of our directors felt that architectural correction within the Operating Rooms, Delivery Rooms, etc., was indicated and this was accomplished prior to opening the hospital.

In sampling areas within the new building prior to opening, we were most pleased with the general colony counts in the "supply and decontamination" center as well as the Operating Room suite, but suddenly a flaw appeared. Fortunately, before surgery commenced, the overhead tracts of the O.R. lights were found to be repeatedly bacteriologically filthy. With the use of a phenolic cleaner with some residual power and with the discontinuance of overhead work, the area came into our normal count level and once all other areas checked out, the Operating Rooms were opened. One can easily imagine patients under these lights with foamites dropping in on the open abdomen from above. Needless to say, we continue our Rodac® plates and exposure plates in the Operating Rooms and Delivery Rooms despite the A.H.A.'s absurd dictum. Fortunately for us, Dr. Bertha Litsky of the Bingham Associates has confirmed our beliefs in this direction, for in these endeavors we have had no administrative cooperation and this good outside influence has been the necessary prod.

A later Operating Room problem arose which showed up on exposure plates. Work was being done on a gas evacuation pump and some piping was required in the area above the Operating Room. Apparently the activity in this area caused an increase in fallout, even when workmen were not present, but, post-installation, complete cleaning was required and then testing with both Rodac and exposure plates assured us of the safety within the rooms.

The Nursery was another area where contamination was most persistent. The common bench for washing and changing of the normal infants was found to have very high counts. Despite cleaning

with the normal Sani-Master® quaternary ammonium product, the counts remained essentially unchanged. The main offenders that this product did not seem to control were the gram-negative bacilli as *Pseudomonas* and some varieties of the *E. Coli* group. When attendants changed to Staphene® as cleaning agent and scrubbed with great regularity, the bench cleaned up remarkably and counts came down to "our" normals. Without our knowledge, after opening, the nursery area ran out of Staphene and the attendants returned to the use of the former products as the director did not order more Staphene. With our routine checking, it was noted by the bacteriologist that the counts were again very high (over 100 col./plate.) At our insistence the use of Staphene (-benzyl p-chlorophenol phenyl-phenol p-tertiary amylphenol 2, 2 methylene bis-3,4,6 trichlorophenol) was reinstated as used in our former nursery and this brought the counts to normal levels. The bench and weigh-in sector now have counts at less than 20 col./plate but the sink where physicians wash prior to examining the babies does occasionally rise to the 36-40 col./plate.

The kitchen area, which in our former facility was one of the cleanest and most sterile areas, became a major problem. Particular spots where some food spillage is bound to occur as the fryolator and pastry benches showed marked overgrowth of the plates — always above 100 col. Since this had not occurred in the previous hospital, we looked for the change in conditions. It was found that a new cleaning agent, Mikrokleen® (Butoxypolypropopolyethoxyethanol iodine) was being used. Immediately post cleaning, the benches were good, but this solution had no holding power and within 1-2 hours organisms in overwhelming numbers appeared. On review of these problems with the Manager and Chef, it was decided to return to the original cleaning agent: Microquat® (Alkyl dimethyl benzyl ammonium chloride tri-sodium ethylene diamine tetraacetate.) Within a few days the counts became normal and have remained there with very few exceptions since that time (about a six-months period). Even when food particles are present on the benches, the counts remain normal so we have become convinced that thorough cleaning regularly with Microquat inhibits the bacteria from growing even in these constantly exposed places.

Now at eight months after opening, the routine culturing of areas, both by Rodac and exposure plates seems to be quite good. One of our delivery rooms gives intermittent troubles and this may be due to persistent moisture on the walls from a roof leak (Again new construction). Since the entire O.R.-Delivery Unit is cleaned in the same way and the other rooms remain excellent, one must assume that some other factor or factors remain. The S.P.D. gallery stays in excellent control and sterile packages on random check are "in truth" sterile. One breakdown in our sterilizers occurred within 4 months after opening, but sterilization was car-

ried out via an auxiliary facility with no untoward effects.

Continuous checking of our cardio-pulmonary units shows satisfactory sterility in tubes, connectors and exchange boxes. Similarly, regular checking of the sterilizer strips from the gas sterilizer shows "no growth." Despite these relatively good control results, we continue our vigilance with spot checks in all areas of patient exposure. We also do some monitoring of personnel as "post-scrub" cultures of hands as well as repeat cultures of those same hands once the gloves are removed at the end of an operation. We have compared cultures taken in this manner at the end of 1, 2 and even 4-hour operations and have found essentially no differences if the original scrubbing was adequate. We do not routinely check other sources on personnel, but if an in-hospital infection arises, then N. & T. as well as skin cultures are checked to compare with the offending organism.

Steps taken by administration prior to the new hospital move included the hiring of outside organized housekeeping, laundry and dietary groups. Whether this was done for monetary reasons or in an attempt to help control environmental threats to patients, I do not know. At the outset, this seemed a good measure, but very quickly it became obvious that certain inadequacies existed. No medical staff committee can dictate "solutions" to be used by such "outsiders" nor how the cleaning is to be done and any head of such a committee has no power to change methods approved by administration. Fortunately, in dealing with the dietary department, our wishes were acceded to and protection in this area was reestablished. Our studies in regard to Microquat held up well. After consultation with Dr. Litsky, 4-5 months after the fact, we learned that Microquat was one of the best of the quaternary ammonium compounds and the improvement we encountered should have been expected.

Despite our warnings, after nine months in the new arena, wall counts in certain sectors as nursery and delivery rooms continue to be very high at times, in fact, often overgrown and must indeed pose a constant threat to patients and perhaps to personnel. It thus becomes imperative to state that no Infection Control Committee of the medical staff should undertake the job of monitoring a new or renovated health care facility unless it has the power to act and not simply to report. When administration, having hired outside experts who function primarily to make money, has completely tied the hands of an in-hospital control group, allowing it only to report the existing problems and requiring from it "written rules" which cannot be enforced, then such a Committee cannot take the necessary steps to insure hospital safety and should, in fact, disband.

There is little joy in saying, "I told you so," for morbidity and mortality can be reduced by active deeds resulting from adequate careful, thoughtful

monitoring when reporting results in subsequent action. As Dr. Litsky stated to us, simply walking about with culture tubes may encourage cleanliness and may stimulate hospital personnel into better habits. Once physicians no longer find important the protection of their own patients and allow so-called policing to pass into the hands of those less conscious of the inherent dangers, then the greater part of environmental safety will have passed away. Persons in the "business" of hospitals are there for economic reasons and to contain costs and cannot be equally on the side of patient protection and better care.

To draw a conclusion from a single experience is not only presumptive, but downright ridiculous. However, I do not think it out of line to point certain directions physicians should follow when they are about to occupy a new or renovated health facility:

1. Architecture should be screened carefully for sources of contamination such as: air circulation patterns, uncleanable areas and overactivity in critical areas where design has made such body motion necessary.

2. Specific and routine culturing of all areas having to do with patient exposure. These should include both contact plates and time-exposure plates. Criteria for allowable counts must be established for specific locales even if it means using a prior institution as a baseline.

3. Evaluation of agents for cleaning as well as evaluation of the cleaning methods must be done before the doors are opened.

4. Repeated and continuous checking of the

sterilizing equipment and methods must be part of the pre-opening detail with the knowledge that such checks continue indefinitely. Sterility checks of "sterile packages" prior to outdating must be done to insure that the packaging as well as the sterilization procedure is adequate.

5. Physicians must be made conscious of their duties in this direction and must have the power to change ill-advised regulations, for it is truly for the protection of their patients that these things are done and not to abide by regulations imposed by the A.H.A. or to satisfy administration's desires not to be sued.

ACKNOWLEDGMENTS

I would like to thank the Bacteriology Department under Dr. Lloyd Roberts, particularly Robert Smith and Pamela Rice, for their continuous aid in obtaining and recording our control studies.

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R.F.D. 2, Lincolnville, Maine 04849

Reminder to M.M.A. Members

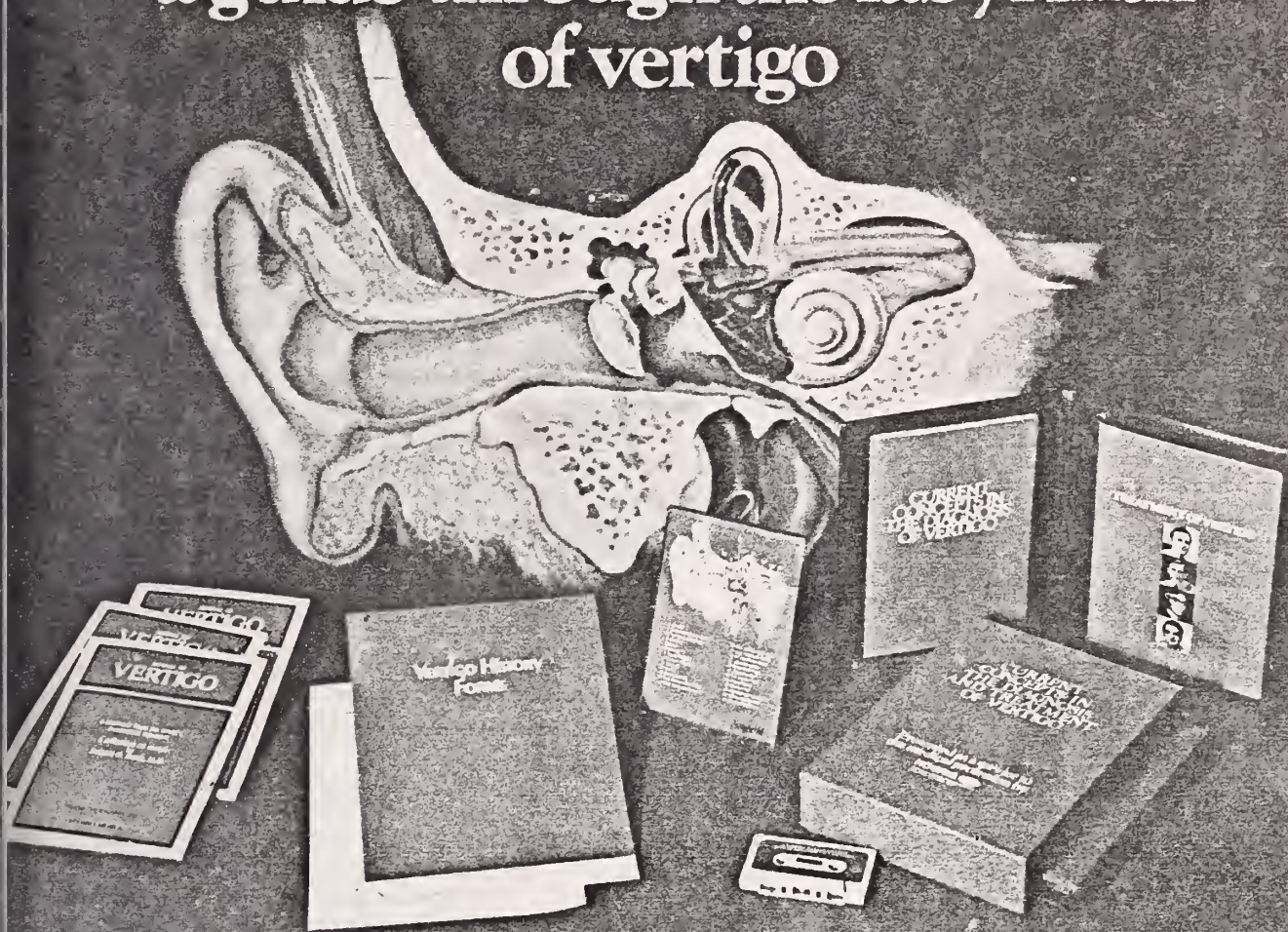
CONTINUING MEDICAL EDUCATION ACTIVITY REPORT

The bylaws of the Maine Medical Association were amended in June of 1973 as follows: Chapter I, Section 11, — "Each member of the Maine Medical Association shall be required to report his activities in continuing medical education every year according to a format provided by the Committee on Continuing Medical Education."

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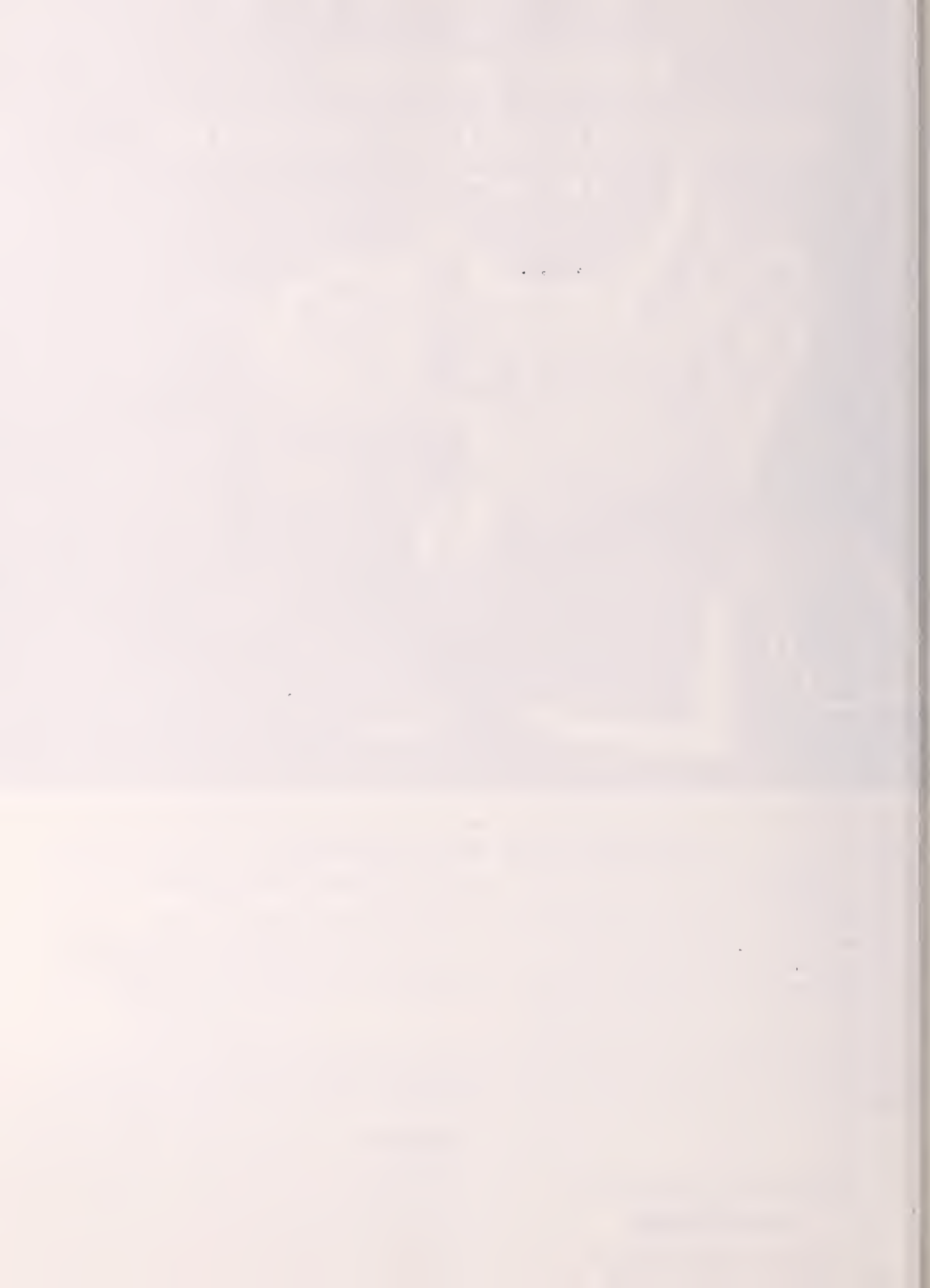
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Health Planning for Primary Care in Rural Shortage Areas

ROBERT M. TRUE, M.D.,* ROBERT E. CAVEN, M.D.** and RICHARD P. FRECHETTE†

ABSTRACT

An in depth study of Maine primary care physicians, using nationally accepted standards for physician distribution, demonstrated that there is a marked and significant shortage of general internists, pediatric generalists, and family physicians. Furthermore, there is an aging and aged physician population that is increasingly unable to meet the primary health care demands of the people of Maine. There is a geographic maldistribution as well as a maldistribution by specialty. Maine's postdoctoral training programs and approaches to physician recruitment are only partially meeting this need. These findings are contrary to frequently quoted statistics utilized by various federal and state agencies. Various solutions are proposed to improve the critical situation of numbers and distribution.

The medical care problems faced by the State of Maine are shared by other rural states and provinces in this country and Canada. The most pressing medical problem facing this area is our inability to provide comprehensive and high level primary medical care for all inhabitants of the State.

A definition, recently approved by the Board of Directors of the American Academy of Family Physicians, refers to primary care as . . . "a type of medical care delivery which emphasizes first contact care and assumes ongoing responsibility for the patient in both health maintenance and therapy of disease. It is personal care involving a unique interaction and communication between the patient and the physician. It is comprehensive in scope and includes the overall coordination of the care of the patients' health problems be they biological, behavioral, or social. The appropriate use of consultants and community resources is an important part of effective primary care."¹ Maine is suffering a shortage of family physicians, general internists, and pediatric generalists.

A report of the United States Senate Committee

on Labor and Public Welfare in September of 1974,²⁶ quoted James G. Price, M.D., then President of the American Academy of Family Physicians, as reporting that only three states . . . Arizona, Iowa and Maine . . . now have enough family physicians to meet a recommended doctor/patient ratio of 1 to 2,525. This appeared to be a startling inaccuracy when applied to Maine. In reviewing the literature on suggested physician to patient ratios, one finds a range from 8 to 13 per 10,000.^{9,17,20,21,23} These figures are usually based on the median morbidity per 1,000 residents in an "average community." The figure of "8" should be considered quite conservative and represents the number most frequently utilized by other studies.^{9,20} It is certainly less than the 13.3 recommended by Schonfeld, Heston, and Falk in 1972 and somewhat more than that quoted in the *Congressional Record*. A balance of 62½% family physicians, 12½% pediatricians, and 25% internists was a universal recommendation of the three documented studies reviewed.

National studies carried out between 1953 and 1971 by the U.S. Department of Health, Education and Welfare⁷ showed an increasing demand for ambulatory services and the lack of access to this important care for significant segments of the population. The proportion of people who require the services of a physician has increased in a rather spectacular manner, particularly the aging and the aged patient. Hospitals have been increasingly used for primary care in the urban areas while those who live in rural areas have limited access to any service whatsoever.

Studies sponsored by the Southern Maine Comprehensive Health Association, Inc.¹⁹ showed that patients with low incomes tend to under-utilize preventive health and postpone action when symptoms of ill health appear. Higher income patients, with greater access to medical care, complain of the need for more services. A health study commissioned by the Joint Ambulatory Care Committee of the Southern Maine Comprehensive Health Association and Maine's Regional Medical Program stated . . . "there is little question that changes are needed in the way ambulatory services are delivered . . . it became evident that there was no reliable data as to use and delivery of ambulatory services. . . ."²

The people of the State of Maine are faced with a dual problem involving both a paucity of primary care physicians and geographic maldistribution. The problem is further compounded by both the size and rural nature of the State as well as the lack

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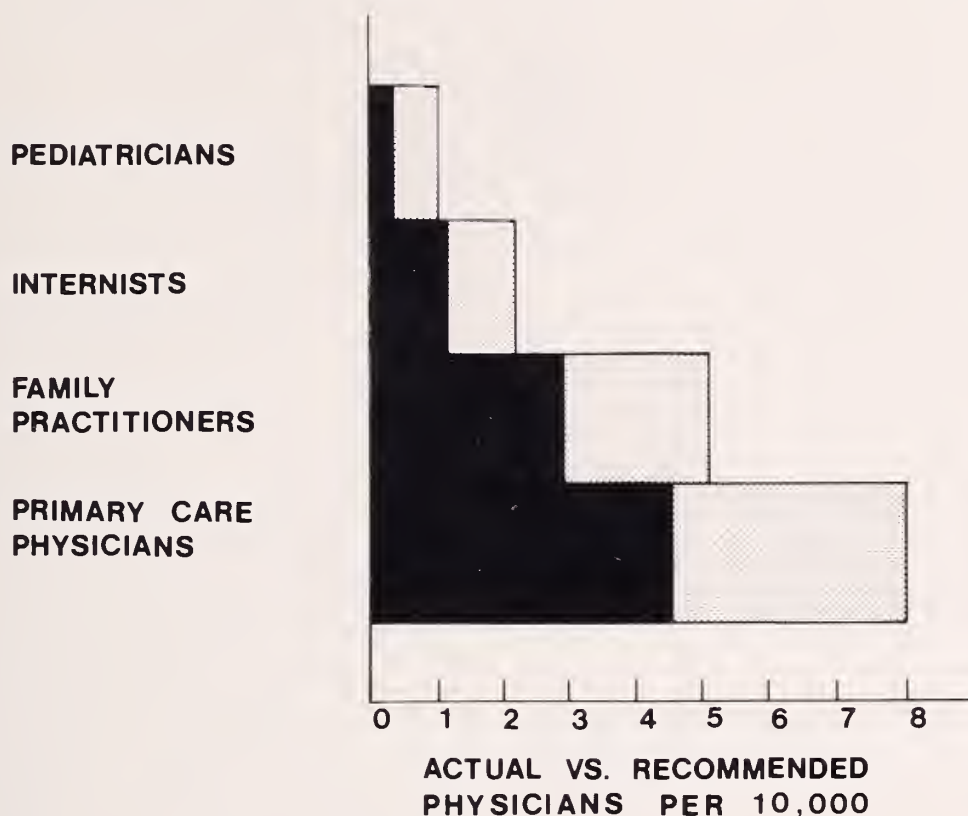
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STATEWIDE NEED FOR PRIMARY CARE PHYSICIANS



of a medical school and an insufficient number of primary care residency positions. The existing Family Practice, Internal Medicine, and Pediatric Residency Training Programs within the State are now graduating sixteen family physicians, five internists, and four pediatricians each year. This is a significant step in the right direction but is not the answer to the problem. If each and every one of these graduates were to remain within the State of Maine, this number would barely allow for the current loss by death, disability, and retirement of primary care physicians now in practice. It would not supply the pool of primary care physicians needed for adequate health care. For that matter, there would be no assurance that a satisfactory geographic distribution could be attained.

METHODS

In mid-1975, several members of Maine Medical Center's Department of Family Practice decided to embark upon an independent study to evaluate some of these needs. The project, utilizing both a factual and an attitudinal approach, was supplemented by information obtained from various state health planning agencies, the Maine Publicity Bureau, the Maine Medical Association, the Maine Board of Registration of Medicine, the Census Bureau, and a review of the current applicable literature.

A questionnaire was designed to search out fac-

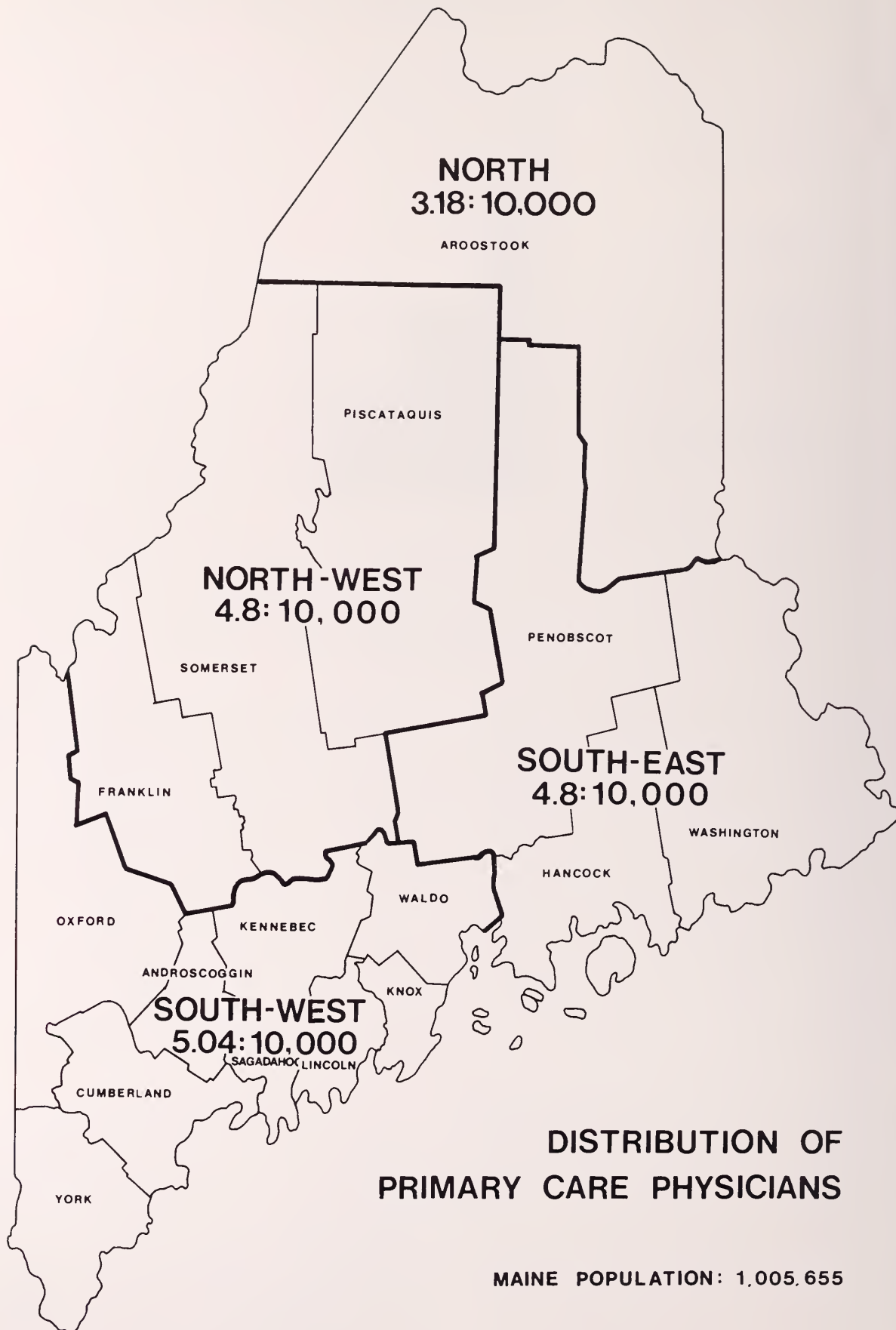
tual data and to evaluate attitudes of practicing primary care physicians. A mailing to all Maine MD's in these categories went out mid-June of 1975, containing questions relating to physicians training and background, as well as their previous contacts with the State of Maine and the New England area. It also sought to determine the major influencing factors leading towards their decision to practice in Maine. Finally, opinions were requested as to how to attract young physicians to rural Maine.

In order to more effectively study the physician shortage, we arbitrarily partitioned the entire State into four major regions, North, Northwest, Southwest and Southeast. Additionally, a county by county study, utilizing the results of the questionnaire as well as information obtained from federal and State sources.

RESULTS AND DISCUSSION

Response to the questionnaire was most encouraging with a total of 57.2% of all primary care physicians completing the questionnaire. Seventy-six and one-half percent of the pediatricians, 57.4% of the internists and 47% of the family physicians returned completed questionnaires.

The figures that were supplied by both the Maine Medical Association and the Maine Board of Registration of Medicine were somewhat misleading since no information was provided regarding the percentage of time spent in active practice. Our



DISTRIBUTION OF PRIMARY CARE PHYSICIANS

MAINE POPULATION: 1,005,655

inventory revealed that there are 437 primary care physicians practicing in Maine. Of the total number of respondents, only 83% are in full-time practice with the remainder working quarter to three-quarter time.

Our studies lead us to believe that almost one licensed primary care physician in 10 is completely retired. Allowing for those physicians that are in part-time practice, we have 411.5 primary care *physician equivalents* now providing care for the people of Maine.

The county by county study showed that only 55% of the State's needs for primary care physicians were currently being met. Only one area, Knox County, exceeded the recommended number of physicians and then only by 3%. The populated Penobscot Bay islands (Knox County) are sufficiently remote as to present a problem despite the overall county average. The remaining counties have 41% to 81.9% of their requirements. Washington County, with an area two and a half times that of Rhode Island and a population of 3.8% that of Rhode Island would have almost enough primary care physicians if all inhabitants lived in one section of the county. Unfortunately, almost ninety percent of the population live in towns of less than 2,500 people.

The Southwest area presents the fewest geographic problems because it is relatively compact. This is reflected in the fact that it has the highest ratio of primary care physicians to patients and has been evaluated at 5.04 per 10,000. This is far below the recommended ratio of 8:10,000.

The Northern area has the greatest deficit with only 3.18 primary care physicians per 10,000 and the remaining two areas were found to have similar problems (See Bar Graphs and Map).

To further illustrate geographic problems, Maine has approximately the same population as Portland, Oregon and exactly the same number of primary care physicians.⁸ Portland, Oregon shares with us the dubious distinction of having 55% of its needed primary care physicians but has the distinct advantage of having only 0.25% the area of the State of Maine. With a year round population of somewhat over one million (1,005,655) residents, and State population projections of over two million in the next twenty years, the problem is further compounded by the fact that Maine's population is more than doubled during the summer months.¹² About half of its total population reside on the Atlantic coastal strip which constitutes 11% of the State's total land mass. Three of every four Maine vacationers are lured to these rocky shores resulting in a seasonal three-fold increase in the population of some of these villages and towns. It is traditional for families of summer visitors to spend their entire vacations in Maine and many of the more affluent families remain for the entire season.^{13,27} It is logical to state that these rapidly rising health care needs place unusual demands on both primary care phy-

sicians and community hospitals during the vacation months.

Continuing projections show that if every over-worked primary care physician now in practice assumed the medical care of the recommended number of patients,^{9,17,20,21} almost 45% of the permanent inhabitants of the State would be without a physician!

To move for a moment from primary care physicians, our studies generated another interesting statistic. Ideally, we should have 1.25 surgical specialists per 10,000 population.²³ We have 2 per 10,000 or 160% of our surgical needs. Additionally, 13.4% of the primary care physicians do general surgery. The major problem here would appear to be one of geographic maldistribution since many Maine counties are surgically underserved.

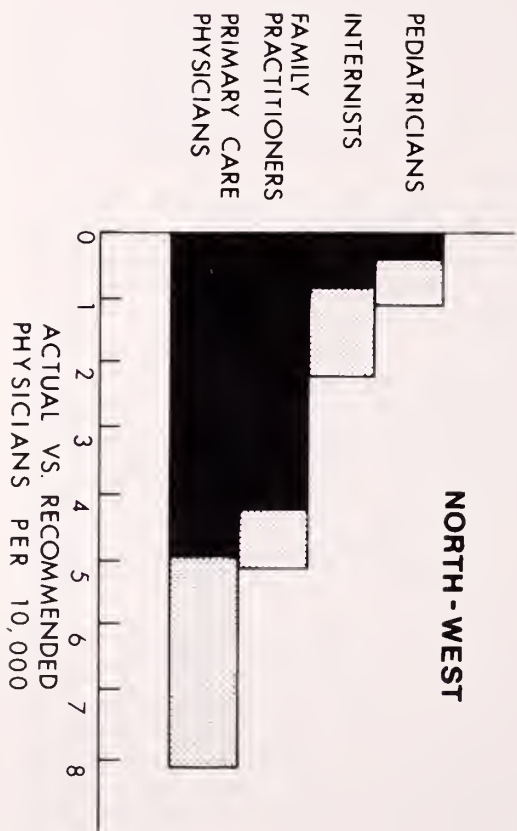
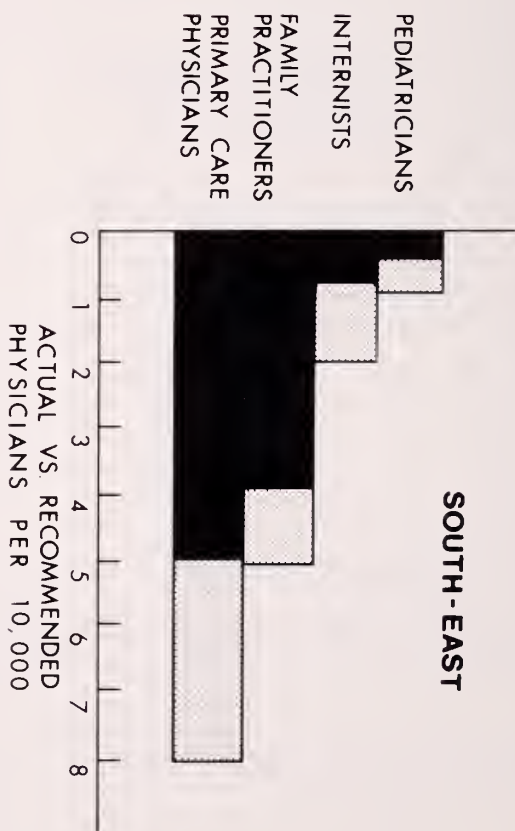
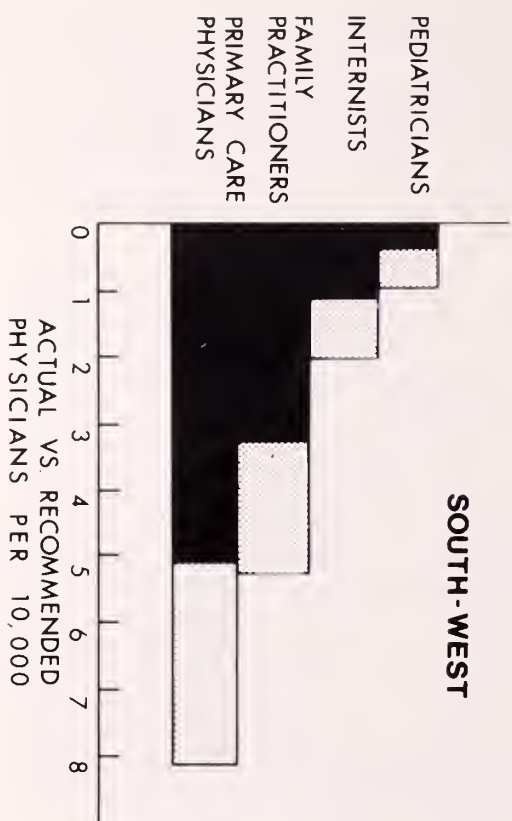
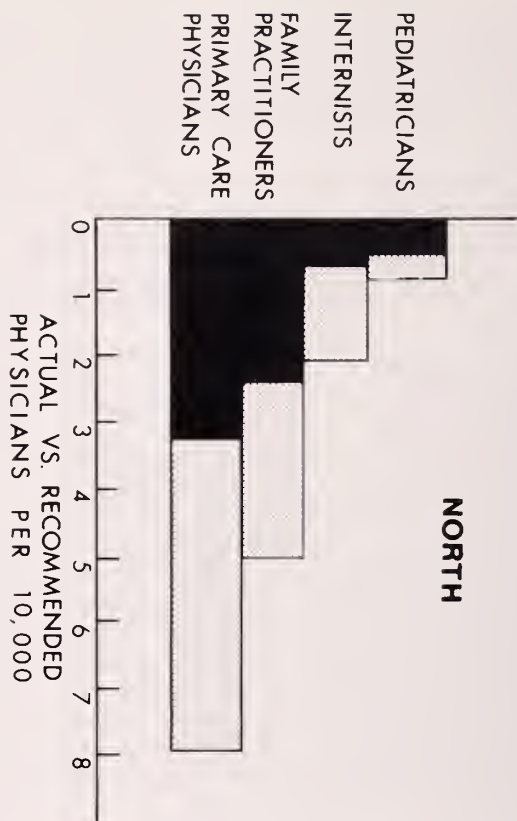
Over 46% of Maine's primary care physicians practice in the twelve Maine cities with populations greater than ten thousand. While predictable, it is significant that two-thirds of the internists and well over one-half of the pediatricians have located their practices in these areas while almost two-thirds of the family physicians practice in the remaining villages and towns. The survey revealed that rural areas had 3.45 primary care physicians per ten thousand, rather than the desired 8 per ten thousand.

Maine could lose a significant percentage of its existing supply of family physicians by 1980. This may be attributed to the fact that 17.7% of the primary care physicians in Maine are over age 65 or will reach their sixty-fifth birthday in 1976. Unspecialized pediatricians and internists are replacing some of the family physicians in the urban/suburban areas but there are virtually no replacements in rural Maine, particularly in the poorer and more sparsely populated regions of the State.²⁴

Urban areas are not without their problems. Many patients, while able to find subspecialty care, cannot find a family physician or, for that matter, a general internist or pediatric generalist. The shortage of family physicians is not confined to the State of Maine but is a problem that is found nationwide.^{1,7,8,26} Rural areas appear to have the greatest need followed by the central cities.¹⁷ The State of Maine will have to produce or attract approximately 36 family physicians, 14 internists, and 7 pediatricians per year in order to meet the demands of health care and to catch up with our population growth. Presently, our production of primary care physicians only meets the attrition rate of a currently inadequate supply.

To meet our present requirements, we need 357 more primary care physicians. Further broken down, this would mean 223 family physicians, 89 internists, and 45 pediatricians. As the population of Maine continues to expand, these figures must increase. It should be noted that this deficit extends to all three of these specialties with Family Practice having the greatest need. The major problem lies in

REGIONAL NEED FOR PRIMARY CARE PHYSICIANS



the rural areas where the population is both low and scattered. It is fairly obvious that every Maine cross-roads town cannot support a physician, but if we consider a regional approach, the location of medical group practices becomes more feasible.

Physicians in rural areas are reaching retirement age at a much higher rate than the younger doctors are replacing them.²⁴ This widens the gap between available medical care and the growing needs of the people.

The overall average age of Maine primary care physicians is 52, five years more than that of the national average.¹⁷ The average family physician is 55, the internist 47, and the pediatrician 50. More than one-third of these physicians are over 55 and less than 10 percent are under 35.

Since 1905, death rates in Maine have been higher than comparable U. S. rates each and every year.²⁶ This has been attributed to a number of causes; namely, that we have a greater proportion of elderly residents resulting in a higher incidence of geriatric diseases as well as an above average number of infant deaths. Although we have many residents aged 65 years and over and more (11.6% in 1970), our share of elderly citizens is still far behind Florida, Arkansas, Nebraska, Iowa, and South Dakota.²² It would seem that some factor other than the numbers of geriatric residents must be involved in Maine's having a higher death rate than the country wide average. In the past two years there has been a significant decrease in infant mortality that seems directly related to the institution of a Neonatal Intensive Care Unit at the Maine Medical Center.

In a 1975 report to the Maine Planning Office,²⁶ a significant percentage of the study commission felt that "... Maine's death rates were higher than the U. S. figure because of our relatively large elderly rural population and lack of an efficient medical care system." The results of our survey indicate that the more optimistic approach can only be realized if the number of primary care physicians the State increases and the geographic distribution of these physicians improves.

To make matters worse, the situation in the U. S. rural areas borders on a crisis. "... there is a higher proportion of people with disabling chronic disease living in farm areas than anywhere else in the nation. There is a greater number of bed disability days suffered per person per year in non-metropolitan areas. In some rural counties, the infant mortality is almost double the national average ... the farming and lumbering accident fatality rate is higher than in any other occupation except mining and construction. Clearly, rural people are not healthier than urban people yet they have fewer physicians." This 1972 country wide study carried out by Cooper *et al*⁶ showed that only 6% of all U. S. medical graduates settled in rural towns.

It has been postulated that the more contact a

physician has with a state the greater the probability for establishment of a practice in that state. In addition, it has been suggested that recent contacts are more influential than earlier experiences.^{14,27} Our study sought to test this theory in two separate manners. The primary method was an investigation into the backgrounds of primary care physicians within the State. They were asked for their own views on the relationship between experience and practice site choice. Our objective was to determine what circumstances most influenced this choice. The results indicate that there is no clear-cut solution to the problem. A myriad of factors affect the graduating residents' decision as to where his years of training will be put to use. The emotional as well as professional ties formed during childhood, college, and medical training combine with a desire for other personal rewards, for economic gain, a relaxing atmosphere, and a compatible life style. Many respondents indicated that they require the professional stimulation provided by a medical center hospital while others expressed the need for recreational resources such as hunting, fishing and skiing. The results of the opinion component of our poll show that 60% of the primary care physicians in Maine believe that graduates of a future Maine Medical School would remain within the State. In addition, 86% feel that experience in Maine's residency training programs increases the likelihood of physicians remaining in the State. The greatest influence apparently came from the physicians' educational experiences. Ninety-three and one-tenth percent of the primary care physicians practicing in Maine had some professional training in the New England area. Of these, 47 percent had experience in the State of Maine. The effect of spending one's formative years, premedical, and medical education in an area as well as postdoctoral training are all of extreme importance. A great deal of the medical literature has been devoted to arguments over which is most influential. Taylor²² suggests that the size of the place of birth or early environment is most important while Briech⁴ believes that medical school influences are most important. Petersdorf¹⁸ argues in favor of postdoctoral training and Cooper⁶ places equal emphasis on all three. Yett and Sloan,²⁷ in a study performed in the Illinois medical education system, gave minor importance to doctoral training alone and emphasized that, in their study, 86% of those who received their MD and postdoctoral training in the state of their birth remained within that state to practice medicine.

The five states without a medical school are Alaska, Idaho, Montana, Delaware, and Maine. Maine has the lowest percentage of its population going to medical school with a ratio of 1 per 40,000 population. This certainly could influence not only the production of more physicians but also affect immigration patterns. It is difficult to measure the intellectual attraction of a medical school. In a re-

port to Maine's Comprehensive Planning Council,¹³ Mooz stated: "The concurrent development of medical resources within the State would increase its attractiveness to top-quality out-of-state personnel." The report concluded that a medical school would "reduce the isolation of rural practice" and provide an "enhanced communications system which would increase the informational and conferral resources available to all physicians."

Because of Maine's economic situation and the political climate in the State, the legislature's bill for a medical school was vetoed in 1975. This increased the need for the further expansion and development of primary care residencies within the State.

We note that physicians born prior to 1930 were influenced to the greatest extent by their place of birth while those born after 1930 had a tendency to locate near the area of their postdoctoral training. This was evident in both their selection of practice site and in their opinions. This confirms one of our original beliefs; namely, that the severe doctor shortage throughout the State and, for that matter, the country, would be much improved by setting up residency training programs in areas of need. There would be two benefits from this approach. The very fact of setting up the program would provide medical care for underserved areas and would continue to supply much needed medical manpower for the State. Maine, at the present time, has primary care residencies at the Maine Medical Center in the southern area, in the Central Maine area involving a conglomerate of five hospitals, and further north at the Eastern Maine Medical Center in Bangor. Projecting needs for the State based upon the current supply of physicians, the number of residency training programs, physician immigration trends, and the needs of physicians based upon a ratio of 8 primary care physicians for every 10,000 people, we are faced with a somewhat startling bit of information. Supply could meet the need in approximately twenty years, but only if there is no increase in population. It is questionable that Maine can afford to wait and certainly unlikely that there will be no increase in population. We have considered only a gradual straight line increase in population but predictions by various State planners indicate that the rise will be greater.¹²

Foreign medical graduates make up approximately 21.6% of Maine's primary care resources, with 14% having been trained in Canada. Even if one grants the premise that FMG's are meeting some of the primary health care needs, we are not guaranteed that this is a perpetual resource.

The inadequacies in medical care resulting from poor physician distribution might well be corrected by developing the concept of catchment area group practices. Although four or five rural communities adjacent to one another may not be individually large enough to support a single physician, when considered as a single unit, they might very well

support a group practice of as many as three physicians. Group practice in a catchment area brings benefits to both the communities involved and the physicians. The community is supplied with much needed medical services and the group practice brings the physician the professional stimulation that he needs through contact and consultation with his peers. In addition, the group provides the opportunity to take time off for continuing medical education, rest and recreation and provides the inhabitants with an ongoing assurance of continuous coverage.

Communities wanting and needing physicians should not look upon this report or new programs as a cure for their ills. They must look to themselves and make their localities as attractive as possible. Physicians will rarely accept professional isolation and 24-hour work days 365 days a year. "Communities accepting the group practice concept are more apt to attract physicians."¹⁶ Almost sixty-seven percent of all Maine physicians are in solo practice. Physicians prefer to move their families into towns that are alert, progressive, and a pleasant place to live. They are understandably reluctant to sacrifice their children to a poor educational system. This area approach to practice rather than a physician for each community could do much to improve the situation, particularly in rural areas.

CONCLUSIONS

Maine is faced with a scarcity of primary care physicians and this population is weighted in favor of the older age category, with very few in the under 35 age group. It would be appropriate to encourage younger physicians to practice within the State, especially those under 35 who will fill the vacancies left by those retiring or restricting their practices. The following points might be considered as a guide for a structured program of recruitment:

- A. The first task is to define and agree upon the basic objective of any recruitment program in terms of numbers; namely, the balance of family physicians, pediatricians, and general internists to best serve the areas of need.
- B. Specialties and ages of physicians are considerations which are most commonly neglected in planning. Studies of primary care resources need to be carried out both on a Statewide basis and at a local level.
- C. Studies should be designed to determine the following: how many new family physicians should be recruited; how many traditional specialists and of what types; is the community large enough to support these people; and can referrals from other communities be expected? These studies should then result in *selective* recruitment.
- D. State and local recruitment committees should be formed with both physician and lay representation. Residency training program directors should be consulted as well

as professors in selected medical schools. Contacts should not be limited to the area in which the state is located.

There is no formula for complete success in locating physicians for underserved areas but a selective process should have a greater chance for success than the happenstance approach. It is important to add to the number of physicians in an orderly manner and to maintain an appropriate balance of clinical service in all shortage areas of the United States.

Residency training programs are bringing new physicians into the State, but currently, at a rate that is inadequate to meet the need. Residency programs are only part of the total answer. Changes are needed at all levels of medical training in order to affect a real solution. We are presently faced with a relative abundance in many medical disciplines. Our supply of physicians providing the various fragments of care both on a secondary and a tertiary level is contrasted by a severe shortage of those physicians working in the front lines. The complete solution to this problem must stem from a reorientation that begins in the medical school.

The maldistribution by specialty might be traced to medical schools encouraging training in subspecialties and frequently having inadequate and poorly structured family practice electives. This tends to encourage the student to enter the already over supplied subspecialties.^{5,18} Attitudinal changes for medical faculties are imperative as well as changes in the selection process for applicants applying for medical school admission. A large percentage of the physicians entering family practice come from small communities and surprisingly enough, from large urban inner city areas.^{15,16} Medical schools should take the initiative in a campaign to increase the number of family doctors. Two steps could be taken; namely, increasing the quality and quantity of family practice undergraduate training and electives, and secondarily, consideration by admissions committees of students who are more apt to enter the broader disciplines after graduation. Medical students could be motivated towards primary care by the development of stimulating undergraduate programs in family practice, internal medicine, and pediatrics.

The shortage of primary care physicians is not a problem that will go away by itself. It is not a problem that can be debated out of existence. It is only through positive action now that we can hope to provide our people with comprehensive and continuing medical care.

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Gynecomastia In Neurofibromatosis

Report of a Case

MICHAEL A. LACOMBE, M.D.*

ABSTRACT

A forty-year-old man with neurofibromatosis and unilateral gynecomastia, the latter presumably secondary to lipomatosis, is believed to be the first case reported of non-hormonal induced gynecomastia in von Recklinghausen's disease. This patient's melanotic macule and gynecomastia illustrate the difficulty in distinguishing neurofibromatosis from Albright's syndrome.

Gynecomastia in association with neurofibromatosis is exceedingly rare. Thannhauser,¹ in disputing the validity of Albright's polyostotic fibrous dysplasia as a clinical entity, cited two cases with such an association. One, a male with true sexual precocity and gynecomastia, presumably, according to Albright,² had a hypothalamic neurofibroma. Thannhauser's second patient with neurofibromatosis and gynecomastia also had acromegaly, a condition known to predispose to gynecomastia. Reviews of gynecomastia³⁻¹¹ and of neurofibromatosis¹²⁻¹⁶ have reported no instances of association of the two entities. The following case is believed to be the first reported case after Thannhauser's of gynecomastia in neurofibromatosis, and the first instance of non-hormonal induced gynecomastia in association with neurofibromatosis. It is atypical in other aspects as well.

CASE REPORT

Mr. A.T. is a forty-year-old man referred for evaluation of mild hypertension. Physical examination revealed right unilateral gynecomastia (Figure 1). Superimposed were two skin lesions: a single, large melanotic macule which crossed the midline and had irregular, "coast of Maine" borders (Figure 2), and a nodular, plexiform lesion extending into the right axilla. The consistency of the right breast matched that of a single 4 x 4 cm. lipoma found at the postero-inferior border of the macule (Figure 2). The patient said that the breast enlargement had been present since early childhood. He denied any premature sexual development and had had no exposure to digitalis, reserpine, ergot, testosterone, estrogens, phenothiazines, phenytoin, INH, methyl dopa or spironolactone, drugs known to induce gynecomastia. He had no history of tuberculosis, syphilis, cirrhosis, gout, rheumatoid arthritis, lymphogranuloma venereum or ulcerative colitis, all of which are associated with gynecomastia.⁶ Repeated annual physical examinations had shown the patient to be normotensive. His blood pressure never exceeded 140/96, i.e., there was no evidence of severe, prolonged hypertension known to predispose to breast enlargement.⁸

The patient related an intriguing family history, initially denying similar "birth marks," skin tumors or breast enlargement in other family members, but then mentioning that his only sibling had died of a brain tumor at sixteen. He admitted that one of his children had copious freckling and cafe-au-lait spots and that his father and paternal grandfather also shared these skin lesions.

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Fig. 1. The single, confluent, melanotic macule with irregular borders is classically characteristic of Albright's syndrome. Note the nodular, plexiform lesions on the upper right breast.

Urinary levels for vanillylmandelic acid were 10.6, 5.7 and 9.4 mg/24 hours. Urinary metanephrine was 1.54 mg/24 hours. Skin biopsy of the nodular plexus demonstrated confluent neurofibromata. Radiographic exam disclosed no evidence of bone cysts. Multiple serum calciums were normal.

DISCUSSION

Reviews of gynecomastia infrequently mention neurofibromatosis as a cause, presumably on the basis of Thannhauser's paper.¹ Extensive review of the literature yields no case report of non-hormonal induced gynecomastia in a patient with neurofibromatosis. Ottow¹⁷ described two women with discrete neurofibromata of the skin and areolar tissue without generalized breast enlargement, and Haagensen¹⁸ reported a similar case. Preston et al¹⁴ cited one male patient with bilateral gynecomastia and "endocrine dysfunction." The extensive review by Sirtori⁵ includes a photograph of a male patient with asymmetric, bilateral gynecomastia and a "coast of California" melanotic macule. The



Fig. 2. A lipoma is seen at the inferior border of the macule.

photograph is not discussed, nor neurofibromatosis mentioned however. Mr. A.T. is the first case reported of non-hormonal induced gynecomastia in association with neurofibromatosis. Lipomas are associated with unilateral gynecomastia¹¹ and with neurofibromatosis;¹² one may assume, with the lipoma as seen in Figure 2, that Mr. A.T.'s gynecomastia is secondary to lipomatosis.

Furthermore, Mr. A.T. has features of both Albright's syndrome and von Recklinghausen's disease, and superficially might have supported Thannhauser's thesis that the two entities were really the same disease. The single, irregularly bordered melanotic macule has been classically associated with Albright's syndrome. Its appearance in this patient emphasizes the indistinguishable nature of melanotic macules in the two syndromes, as shown by Benedict et al.¹⁹ An additional feature of Albright's syndrome is the patient's gynecomastia, which has been reported, albeit rarely, in males with the disease.²⁰ In contradistinction, the family history, axillary freckling and nodular, plexiform skin lesion, which occurred in 16% of cases in Crowe's series,¹² are typical of neurofibromatosis. Thannhauser¹ had maintained that "Albright's syndrome" was simply neurofibromatosis with primary hyperparathyroidism and resultant fibrous dysplasia of bone. Albright² cited classical differences in the skin lesions, and absence of cutane-

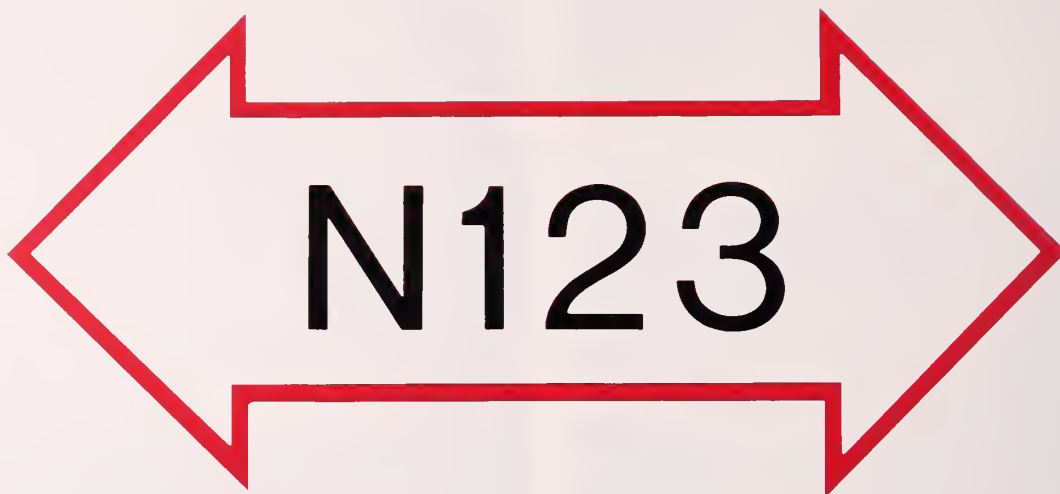
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Fig. 3. Plexiform neurofibromata, seen in a minority of cases of von Recklinghausen's disease.



Fig. 4. Posterior view shows the "coast of Maine" borders and lipoma at inferior margin of skin lesion.



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Beta-Blockers in Hypertension

A Review

KIM L. KELLY, Pharm.D.

Understanding of the pharmacology, pharmacokinetics, and clinical actions of beta-adrenergic blockers has increased greatly over the last 5 years. Indications for their use have become more numerous, while their approval for use in many situations has lagged.¹⁻⁵ The cardiovascular effects of the beta-blocking agents have been studied since the original discovery of dichloroisoproterenol. However, the specific credit for elucidation of the hypotensive effect of the beta-blocking drugs largely goes to Prichard,⁶ and Prichard and Gillam.⁷ Much attention has been focused on the problem of which beta-blocker is most appropriate for use in the control of hypertension. This review summarizes recent work concerning mechanisms of action, clinical use and untoward reactions of the beta blockers, with particular attention to the role of these agents in the treatment of hypertension.

MECHANISMS OF ACTION

There are several proposed mechanisms for the antihypertensive effect of beta-blocking agents. These include reduction of cardiac output (primarily through a reduction in heart rate),^{8,9} a reduction in plasma renin activity,^{10,11} and a central activity.^{12,13}

The Heart

Beta-adrenergic blockade decreases heart rate and cardiac output.^{1,9,14-16} Beta-adrenergic blocking agents also lower blood pressure.^{5,12,17} Several authors have connected these two events in a cause-and-effect relationship,^{9,14,18} but reduction of cardiac output does not entirely account for the antihypertensive effect.^{15,19,20} The reasons for this are as follows:

1. While intravenous administration of propranolol reduces cardiac output, it does not significantly reduce arterial pressure.
2. Non-responders to propranolol have the same decrease in heart rate and cardiac output as patients who respond to the drug.
3. Finally, if a decrease in cardiac output were

the major reason for the hypotensive effect, a correlation should exist between reduction of pressure and pretreatment cardiac index. This expected correlation has not been found.¹⁵ Also, one beta-blocker, timolol, decreases blood pressure with little or no effect on cardiac output.^{20,21} However, cardiac effects still may play some role in the anti-hypertensive effect. Ibrahim²² demonstrated subgroups of hypertensives with increased cardio-adrenergic drive, and proposed that these patients may constitute a subgroup in whom a hyperdynamic circulation contributes to elevating the blood pressure. However, in further studies of these patients with "hyperkinetic essential hypertension," he reported that propranolol treatment reduces symptomatology but does not predictably lower blood pressure.²³

Of interest is the decrease in plasma volume associated with beta-blockade during short and long term treatment.²⁰ No relationship was observed between the reduction in plasma volume and alterations in total peripheral resistance, nor was there a significant correlation with a decrease in cardiac output.

Renin

The role of the renin-angiotensin-aldosterone system in essential hypertension has generated considerable concern.^{24,25} Most beta-blocking agents suppress renin secretion,^{10,11,26-29} which has led some authors to associate the hypotensive effect with the effect on renin.^{11,24,28,30}

It is not established whether the sympathetically-mediated release of renin from the kidney is the result of intra-renal or extra-renal beta adrenergic receptors. At least one study suggested that alpha-adrenergic blockade decreased renin secretion.²⁶ Whatever the adrenergic mediator (and its receptor), or wherever it is located, beta adrenergic blockade will suppress the release of renin due either to upright posture, sodium deprivation, or isoproterenol infusion.³¹ In experimental animals the autonomic release of renin can be inhibited centrally;³¹ this central effect may also play a role in humans.

Most antihypertensive drugs increase plasma renin activity.^{31,32} Beta adrenergic blockade decreases renin levels, both drug-stimulated,³³ and in renovascular hypertension.¹⁰ However, one study

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suggested that beta blockade may not suppress renin release in patients who receive concomitant diuretic therapy.³⁴ Although blood levels were not reported in this study, the dose (160 mg per day) should have been adequate to suppress renin release.¹⁰ Propranolol-associated changes in plasma renin were highly variable, and not statistically significant. Furthermore, they did not seem to correlate with the antihypertensive effect. Fourteen of 20 patients achieved appreciable reductions in blood pressure with little or no change in plasma renin activity.

A more fundamental problem is that of the role that renin plays in the majority of patients with essential hypertension. Essential hypertension can be divided into "low," "normal," and "high" renin varieties. Prognostic estimates based on this differentiation can be made regarding severity of the disease and the ease of treatment with various regimens.^{11,23,24} In patients with high renin essential hypertension, renin probably does contribute to elevation of blood pressure, since reduction of pressure occurs in such patients following administration of antagonists to angiotensin II. However, high renal perfusion pressure associated with high blood pressure may contribute to hyperreninemia.³⁵

Understanding of the "low renin" hypertensive population has been modified recently.³⁶ The proportions of patients in the low renin group have varied greatly since renin levels vary from time to time in these individuals.³⁵ There is no clear boundary between low- and normal-renin groups.³⁶ Indeed, low renin levels may simply represent a secondary response to prolonged elevations of blood pressure.^{37,38}

The renin hypotheses of essential hypertension are obscured by the poor correlation between plasma renin levels and antihypertensive effect,³⁹⁻⁴¹ the fact that in patients with renovascular hypotension beta blockade reduced plasma renin activity (PRA) but did not change blood pressure,¹⁰ the demonstration of a hypotensive effect from practolol without significant alteration of PRA,⁴² and the possibility, although controversial,⁴³ that pindolol reduces blood pressure but *elevates* plasma renin levels in humans⁴⁴ and experimental animals.⁴⁵

Central Nervous System

Beta blockers may have a central hypotensive effect.^{12,19,46} Penetration of various beta blocking agents into the central nervous system (CNS) has led to their utilization in the field of psychiatry.⁴⁷ CNS penetration has been demonstrated for propranolol^{13,46-48} and assumed for many of the other beta-blockers due to their CNS effects or side effects.⁴⁷ Lipid-water partition coefficients for a number of beta-blockers are not available, but most of these agents appear to be sufficiently lipophilic to penetrate the CNS.^{49,50} Although practolol appears to enter the CNS less readily than propranolol^{51,52} at least one author has noted "quite a number of pa-

tients on practolol have vivid dreams . . ." when high doses are used chronically in patients with hypertension.¹⁷

Of considerable importance is the fate of metabolites of the beta-blockers. Paterson⁵³ studied the distribution of ¹⁴C-propranolol and two major metabolites, 4-hydroxypropranolol and naphthoxy-lactic acid. Relatively high serum levels of unidentified metabolites were noted, and this level decayed with a longer half-life than the parent compound or 4-hydroxypropranolol. Such metabolites may have CNS activity. Saelens et al¹³ have identified propranolol glycol as a human metabolite of propranolol. In experimental animals, propranolol glycol was more potent in lowering blood pressure than propranolol, and the delay in anticonvulsant activity of propranolol could be attributed to the time required for formation of the glycol metabolite. These authors cited other workers who demonstrated similar metabolites of oxprenolol and other beta-blockers. This may be the metabolite that Garvey and Ram⁴⁶ noted in high concentration in the CNS.

A summary of the properties of beta adrenergic blocking agents and their effects on the heart, renin, and the CNS can be found in Table 1.^{54,55}

CLINICAL UTILIZATION AND ADVANTAGES

Efficacy

Although no beta blocking agents are currently approved for the treatment of hypertension in the United States, the efficacy of beta-blockers is well established.^{5-7,11,12,17,19,30} Ongoing work now is mostly aimed at refining therapeutic approaches with these drugs.

Pharmacokinetics

The pharmacokinetics of propranolol are extremely complex.⁵⁶⁻⁵⁹ Propranolol is metabolized to at least 30 different compounds⁵⁶ with different beta-blocking and hypotensive properties. At least two metabolites, propranolol glycol^{13,56} and isopropylamine⁵⁶ have central hypotensive properties.

The conversion of propranolol to isopropylamine is a minor pathway of metabolism and accounts for only two percent of the administered dose in the rat.⁶⁰ Thus, it is not presumed to be a significant factor in the hypotensive effect of propranolol in humans. In earlier work with ¹⁴C-propranolol, plasma levels of total radioactivity were nearly twenty times the radioactivity which could be attributed to propranolol and 4-hydroxypropranolol. There are a number of these metabolites of propranolol whose antihypertensive properties are unknown.

Propranolol has been shown to exhibit a significant "first-pass" effect after oral administration,^{61,62} with production of significant quantities of the 4-hydroxy derivative after oral but not intravenous administration.^{58,62} While this derivative has beta-blocking activity roughly equivalent to the

TABLE 1

CLASSIFICATION OF BETA-BLOCKING AGENTS AND PERTINENT PROPERTIES
CLASS I Beta Blockers With Membrane Activity and Intrinsic Beta Stimulation

Generic Name	Trade Name or Other Designation	Membrane Activity	Intrinsic Beta Stimulation	Selectivity		Potency (Blockade of Isoproterenol tachycardia) Propranolol = 1.0	Antihypertensive Potency (Propranolol = 1.0)	Renin Levels	Cardiac Output	CNS Penetration
				β_1	β_2					
dichloroisoproterenol	DCI	+	3	2+	+	0.1				
pronethalol	Alderlin	+	3	2+	+	0.1			◆	
oxprenolol	Trasicor	+	2	2+	+	0.8-	0.8 (5)	◆ (94)		"yes"
alprenolol	Aptine	+	2	2+	+	1.0	1.0 (5)	◆ (28)	◆ (93)	CNS levels = to plasma levels (cats) (95). "anticonvulsant activity" (47)
pindolol	LB 46 Visken	±	2-3 (45)	2+	1-2+		12.3 (5)	◆ (45)		CNS levels (chronic) (46) 4-9 X serum levels

CLASS II Beta Blockers With Membrane Activity But No Intrinsic Beta Stimulation

propranolol	Inderal®	+	0	2+	3+	1.0	1.0	◆	◆	"yes" (47) ... CNS levels plasma levels (46) ... glycol metabolite with good penetration /or locally produced from propranolol (13)
butidrine	—	+	?							"yes" (47)

CLASS III Beta Blockers With Intrinsic Beta Stimulation But No Membrane Activity

Niferalol	Inpea	0	+		0.05 (96)					
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CLASS IV Beta Blockers With No Membrane Activity And No Intrinsic Beta Stimulation

sotalol	MJ-1999	0	0	2+	+	0.1-0.3 (46) (55)			◆ (46)	CNS levels = 1-3 X plasma levels (46)
timolol	MK-950	0	±	+	?	8-10	6 (20)		◆	
practolol	ICI ^{50, 172} Eraldin	0	+	2+	0	0.3-0.5 (12) (55)	0.24	PRA 80% of control ... (45) "No significant decrease ... (42) (dose 20 mg 1V)	◆or◆ (16) (97) (only ◆ in high doses)	"Poor." (47) "Weak if any ... (98) Brain levels = blood levels at 24 hrs. post 1V dose (dogs) (52) " ... Vivid dreams in spite of the fact that practolol is said not to cross the blood-brain barrier. (17) (yes)
metoprolol	H 93/26	±	0	2+	0(±)	0.8-1.0 (99)	0.75	◆ (99)	◆ (100)	(99)

After: Fitzgerald (54) with modifications suggested by Miller (55). Further modified by incorporation of agents with Beta-1 selectivity into the appropriate group. (Groups differentiated by the presence of intrinsic beta stimulation and membrane activity.)

parent compound, its relevance to the hypotensive effect of the drug is unclear since it appears primarily on short-term oral administration of the drug and may have a shorter half-life than the parent drug.⁵⁸ A first-pass effect has also been observed for alprenolol, oxprenolol, metoprolol, and to a minor extent for pindolol.^{56,63}

Practolol is eliminated almost completely by glomerular filtration. Pindolol is eliminated by both metabolism and renal excretion;^{2,64} having an elimination half-life falling between two and six hours. Practolol, has a half-life of 9 to 12 hours after intravenous administration.

Propranolol is highly bound to plasma proteins.

When the levels of drug in the plasma are constant, there is a correlation between the amount of drug bound and the plasma protein concentration.⁵⁷ Thus, patients with a low circulating protein (or albumin) concentration should have a lower percentage of total drug bound to circulating protein. Also, as the total amount of drug present in blood increases, the percentage of total drug bound to protein decreases. The clearance of propranolol holds an inverse relationship to protein binding, all other things being equal. The larger the percentage of free drug in the plasma the higher the half-life. Protein binding in the study of Evans, et al⁵⁷ was determined by equilibrium dialysis with plasma levels of 150 to 180 ng/ml. These levels are slightly higher than the levels of 100 ng/ml suggested as an endpoint by Shand.⁶² However, they may be attained during dosage regimens suggested for use of propranolol in hypertension.^{17,59}

In two studies of the kinetics of propranolol in renal failure, a decrease^{65,66} or no change⁶⁷ in propranolol half-life has been reported. Although certain subtle alterations in the hepatic extraction, volume of distribution and perhaps the rate of absorption do exist,^{65,67} significant modifications of dosage are probably not needed in patients with renal disease. However, as much as a three-fold increase in the level of propranolol "metabolites" has been demonstrated in patients with renal impairment.⁶⁶

Propranolol appears to offer some advantages over other beta blockers with respect to dosage regimens.² Propranolol has a reasonably short elimination half-life (approximately 3 to 4 hours) that may necessitate a four-time-daily dosing regimen,⁶¹ but at high doses the apparent elimination half-life may be prolonged because of a dose-dependent "saturation" kinetic effect.⁵⁹ Additionally, propranolol has some potentially active metabolites whose kinetics in the antihypertensive dosing range have not been fully evaluated. Antihypertensive effects have been demonstrated with twice-daily dosing of propranolol⁶⁸ and pindolol,²³ which is consistent with a prolonged elimination half-life of the parent drugs and/or their metabolites at high doses.

Technological advances now make it possible to monitor blood concentrations of several beta blockers. There is data available relating the antihypertensive effects of alprenolol,⁶⁹ pindolol⁷⁰ and propranolol⁷¹ to their blood concentrations. Many previous studies of propranolol pharmacokinetics may need to be reevaluated in light of recent evidence suggesting that the method of blood collection may spuriously alter blood levels.⁷²

Combinations with Other Drugs

Propranolol has been utilized both alone and in combination with other drugs.^{5,17,30} Most commonly, propranolol has been utilized with a diuretic.

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Contraindications: Patients with known hypersensitivity to the drug.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. As with all CNS-acting drugs, caution patients against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving). Though physical and psychological dependence have rarely been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions), following discontinuation of the drug and similar to those seen with barbiturates, have been reported.

Usage in Pregnancy: Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.

Precautions: In the elderly and debilitated, and in children over six, limit to smallest effective dosage (initially 10 mg or less per day) to preclude ataxia or oversedation, increasing gradually as needed and tolerated. Not recommended in children under six. Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider individual pharmacologic effects, particularly in use of potentiating drugs such as MAO inhibitors and phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions (e.g., excitement, stimulation and acute rage) have been reported in psychiatric patients and hyperactive aggressive children. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship has not been established clinically.

Adverse Reactions: Drowsiness, ataxia and confusion may occur, especially in the elderly and debilitated. These are reversible in most instances by proper dosage adjustment, but are also occasionally observed at the lower dosage ranges. In a few instances syncope has been reported. Also encountered are isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent and generally controlled with dosage reduction; changes in EEG patterns (low-voltage fast activity) may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice and hepatic dysfunction have been reported occasionally, making periodic blood counts and liver function tests advisable during protracted therapy.

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Their effects are synergistic, even though there is no expansion of plasma volume with propranolol therapy.⁷³ Additionally, propranolol has been utilized with vasodilators where it appears to be synergistic in reducing blood pressures and antagonizes the tachycardia and elevations in plasma renin associated with vasodilators.^{30,32,33} Combinations with other antihypertensive drugs have also been used.¹⁷

Many patients can be controlled on propranolol alone or propranolol and a diuretic¹⁷ by titrating the propranolol dose. This leaves a small proportion of patients who may need additional medications with their attendant side effects.⁷⁴

Patient Acceptance and Advantages

Many hypertensive patients are either unaware of their disease or are not receiving adequate treatment. However, among those who are being treated, a major problem is non-compliance with the prescribed regimen.^{75,76} Methods of improving compliance through various educational and facilitative programs are now under study.^{75,77} Compliance is lowest when there are large numbers of medications and multiple doses per day, when patient understanding of the disease is poor, and when there are significant side effects.^{76,78} Side effects of antihypertensive medications on most drug regimens are common,⁷⁹ and undoubtedly contribute to reducing compliance.⁷⁴ Patient acceptance of beta-blocking regimens is usually good. This may be due to their effectiveness and low incidence of side effects, as well as the "tranquilizing" effects noted for several of these agents.⁴⁷

UNTOWARD REACTIONS

Untoward reactions to antihypertensive drugs unfortunately are common and generally make patients on therapy feel worse than when they were not under treatment. Untoward reactions include toxicities which can be harmful to patients or their acceptance of the drug regimen and which generally result in discontinuance of the medication. Untoward reactions also include side effects which may be troublesome to patients but generally do not require discontinuance of the drug and do not generally harm the patient. These are common in the treatment of hypertension but low in incidence with beta-blocking regimens.

Toxicities

Toxicities of the drug are primarily cardiac and respiratory. Cardiac toxicity includes not only blockade of sympathetic support (where this may be necessary in the failing heart) but also conduction abnormalities because of effects on atrio-ventricular conduction.⁸⁰

The effects on the bronchial smooth muscle are also well-known. Beta-2 blockade results in bronchoconstriction. The potency of beta-blockers in blocking the bronchial receptors relates to their beta-2 blocking properties. Agents with little beta-2

effect (see Table 1) may produce less bronchospasm, but this is not always the case. Some authors have taken patients who developed bronchospasm on propranolol, switched them to another beta-blocker with less beta-2 effects, and have obtained an adequate response without the development of bronchospasm.^{17,19}

Immunologic reactions to beta blockers, particularly practolol, have received much recent attention. Immunologic effects of practolol have included a lupus-like syndrome, skin lesions (varying from rash to palmar and plantar hyperkeratosis with dystrophic nail changes), ocular complications (such as keratoconjunctivitis sicca, conjunctival scarring and fibrous metaplasia), and deafness.⁸¹ Lesions associated with the "oculocutaneous syndrome" may regress upon discontinuance of the medication, but may become progressive if not treated.⁸² This type of reaction has been reported rarely in patients taking oxprenolol and propranolol.^{83,84} Studies of the immunoglobulins in patients with the oculocutaneous syndrome and other patients with fibrous metaplasia or skin lesions reveal deposition of IgG in the intracellular spaces of squamous epithelium.⁸⁵ A significant number of these patients also have high titres of antinuclear antibodies of the IgM class.^{82,85}

Other toxicities relate to insulin-dependent diabetics whose counter-regulatory response to hypoglycemia may be attenuated. Central nervous system toxicity has also been observed.⁸⁶⁻⁸⁸

Side Effects

The incidence of side effects with antihypertensive drug regimens is high. A study on guanethidine⁸⁹ showed 19 of 64 patients (34%) developing side effects, with some individuals experiencing more than one. In a study of methyldopa,⁹⁰ 72% showed some side effects, and in 14% the reaction was severe enough to result in discontinuance of the drug. Finally, a survey of several different drug regimens⁷⁹ showed side effects on the order of 20 to 50%. Propranolol, however, has been associated with a lower incidence of side effects in clinical use.^{74,79,81,88} Table 2 is a compilation of reported side effects from three studies in the literature.^{88,91,92} In a total of 2071 patients, the incidence of side effects has been approximately 13%, while the incidence of severe reactions of those requiring the discontinuance of the medication has been approximately 4%. This obviously represents a benefit in patient comfort (and perhaps compliance).

SUMMARY

Beta-blocking agents have actions on the heart, the vascular system and its endogenous control, and the central nervous system. Cardiovascular effects account for only a portion of the effect of beta-blockers in hypertension and are probably not the major mechanism of action. Most beta-blockers lower plasma renin activity, and may be particularly

TABLE 2

INCIDENCE OF SIDE EFFECTS IN PATIENTS TAKING PROPRANOLOL			
	303 Patients (92)	268 Patients (90)	1500 Patients (91)
<i>Complaint</i>			
Cold extremities: including chilblains and Raynaud's phenomenon	25	—	—
Bronchospasm	12	—	8
Indigestion: including nausea and flatulence	12	1	16
Vivid dreams alone	8	—	—
Vivid dreams + insomnia	3	—	—
Insomnia alone	4	—	7
Fatigue or tiredness	10	—	18
Hallucinations (usually visual)	4	—	5
Neurological: including paraesthesias, ataxia, dizziness	4	4	25
Diarrhea	3	—	8
Bradycardia	3	9	2
Depression	2	—	—
L. V. insufficiency	1	3	13
Impotence	—	—	—
Hypotension	—	5	8
Claudication (static)	6	—	—
Claudication (worsening)	8	—	—
Heart block	—	2	2
Fluid retention	—	1	—
Weight gain	—	—	2
Purpura or skin rash	—	—	8
Palpitations	—	—	2
Miscellaneous	—	—	5
	105	25	129
	(29 drug D/C'd)	(8 "life threatening")	(43 drug D/C'd)
GRAND TOTAL 259 — (80 "life threatening drug D/C'd")			
Total patients	2071		
Incidence of side effects	12.5%*		
Incidence of serious side effects	3.8%**		

*Due to the different "complaint" descriptions in each article, some categories may contain complaints rightfully belonging in other categories. Also, methods utilized by the authors to collect this information may have been different enough to make this figure only an approximation of the true incidence of side effects.

**This figure represents the percent of patients exposed to propranolol who developed side effects listed either as "life-threatening" or "drug discontinued", and assumes that the drug was discontinued in 33 patients where serious reactions are reported in reference #91.

useful in patients whose elevated renin levels contribute to hypertension. With proper dosage titration most hypertensive patients could probably be controlled on beta-blockers alone or in combination with a diuretic.

Addendum

Subsequent to submission of this article for publication, the FDA approved propranolol for hypertension in dosages up to 640 mg per day.

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GYNECOMASTIA IN NEUROFIBROMATOSIS: REPORT OF A CASE

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ous fibromata in patients with polyostotic fibrous dysplasia and of bone lesions in neurofibromatosis. Patients such as Mr. A.T. illustrate the difficulty in distinguishing Albright's syndrome from von Recklinghausen's disease on clinical grounds alone.

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The Role of Rural Satellite Practices in Primary Care

STEVEN S. LAZARUS, PH.D.* and PETER F. JEFFRIES, M.D.**

The shortage of primary care services is a major problem in rural areas. Larger communities may have health care providers capable of rendering primary care services in adjacent smaller rural communities. Thus, the distribution of services may be improved by health care organizations developing satellite practices. Data on patient visits to the main and satellite practice units are presented for a private practice with three family practice physicians, two MEDEX and supporting staff. Annual visits from the satellite community to the providers increased from an estimated rate of 45 per thousand to 525 per thousand providing significant, available and accessible ambulatory care services. Data on charges to patients are used to estimate the number of patients who must be seen to cover satellite expenses and salaries with varying combinations of physicians-physicians' assistant staffing patterns in the satellite unit.

A major problem facing small rural communities is a shortage of primary care services. There can be no rural accessible, comprehensive, high quality first care services unless the quantity and distribution of these services are increased. Although small communities under 10,000 perceive a need for a physician and even a community hospital,² there may not be the demand to support full time physician and hospital services. Also, the physician and his family may desire the school system and the physician the style of practice made possible by the more complex medical resources of the larger community.³

Assuming that the rural health care delivery crisis could be partially ameliorated by having physicians (at present predominately in private solo or small group practices) in relatively larger communities offer services in nearby smaller communities; what is the demand for primary care in small rural communities and how can that demand be served by a satellite practice? Several insites to these questions can be gained by examining a case study situation in rural New Hampshire.

METHOD

In September, 1972 a group of family practitioners practicing in a medical professional building adjacent to a 67-bed rural hospital established a second practice site 18 miles away in a town of 2300 with no physician. The physicians were living and practicing in a picturesque, well-to-do New England community at the junction of major cross-roads with fine schools and shopping centers. Although the larger community medically serves a wide catchment area and supports multiple specialists and a modern hospital, the physicians were interested in expanding their practice and thought it

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TABLE 1

SATELLITE AND BASE PRACTICE COMMUNITY CHARACTERISTICS	Base Community Satellite Community	
1970 Town Population	3807	2276
Physicians	18	0
Hospital beds	67	0
Physicians per 1000 population	4.7	0
Median age	29.8	33.5
Percent of population 65 and over	11.3	13.9
Median family income	\$10,670	\$8,350

would be difficult to obtain more patients from the base community (Table I).

The three physicians in the group each practice one day a week in the satellite setting. The satellite has a receptionist, x-ray equipment, and a small laboratory. Beginning April, 1973 the physicians have been practicing with a MEDEX physicians' assistant at the satellite unit.

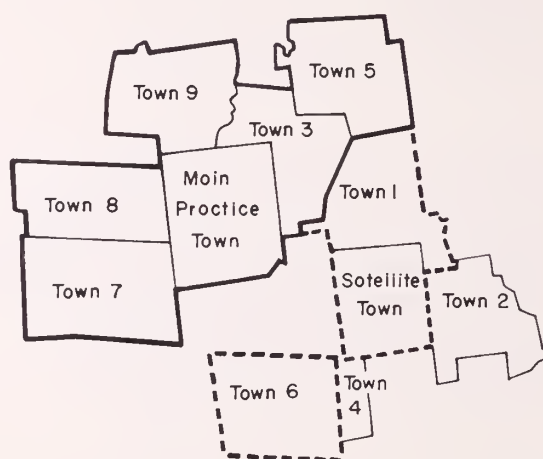
During several two-to-four week periods the providers completed a "Patient Contact Record" (PCR) each time a patient was seen in either practice setting. The PCR was filled out as the care was rendered and contained such information as patient address, age, sex, diagnosis, charge, and treatment and services rendered. During one of the sample periods, PCRs were checked against the appointment log book to ensure that PCRs were obtained on all patients.

RESULTS: PATIENT DEMAND

Within six months of the opening of the second site, the number of patients seen by these physicians from that area more than tripled. The number of visits by patients from each of four towns near the satellite and the satellite town are given in Table 2; for one period prior to and two periods after the establishment of the satellite unit. Most of this increase is due to patients from the town where the satellite is located, but by May, 1973 a significant number of patients appeared from three other near-

Fig. 1

PRACTICE SERVICE AREA Growth from March, 1972 to March, 1973



— March, 1972 (pre satellite)

Service area with more than 250 annual patient encounters per 1000

- - - March, 1973 (post satellite)

Service area added with more than 250 annual patient encounters per 1000

a total of 118 patients (21 percent of office visits at both sites) were seen at the satellite office during 11 office days. The primary towns of patient residence and their patient demand at the satellite are given in Table 3. One hundred and one of the 118 patients travel 12 miles or less to the satellite office. This satellite practice is making a substantial impact in terms of annual visits per capita in the immediate and two neighboring communities (Figure 1). Residents from the satellite office community are also seen in the main office, particularly on days when the satellite is closed. From the last two columns in Table 3, it is seen that the satellite has a much lesser impact on the delivery of health care than the main office in towns more than 12 miles away. This is reasonable since many of these towns are closer to the main office than the satellite and because the main office is open more hours and staffed with more providers than the satellite.

RESULTS: ECONOMIC ANALYSIS

It is difficult to estimate the additional income to the physicians as a result of adding the satellite office because some patients from the satellite area were seen in the main practice before the satellite office opened and some patients from the satellite office are currently seen at the main practice office or the hospital. The marginal costs

TABLE 2

WEEKLY PATIENT VISITS AT ALL SITES BY PLACE OF PATIENT RESIDENCE FOR THREE TIME INTERVALS						
Town	Population	Weekly Patient Visits			Estimated Annual	
		Pre-Satellite 3/72	Post-Satellite 3/73	5/73	Visits/1000 pop. 3/72	3/73
Satellite	2,276	2.0	23.0	15.0	45.7	525.5
Town 1	789	2.0	5.5	3.2	131.8	362.5
Town 2	6,622	0.5	7.5	5.5	3.9	58.9
Town 4	1,587	1.0	2.0	5.0	32.8	65.5
Town 6	1,803	2.5	9.0	5.8	72.1	259.6

by communities. This indicates that the growth in patient visits during the first three months (September to December, 1972) is due primarily to patients from the satellite community; whereas continued growth after that period is due to patients from towns neighboring the satellite town (within 12 miles). By March, 1973 the estimated visits per thousand population rates for several towns neighboring the satellite community have reached the satellite community's pre-satellite rate of 45.7 visits per thousand for March, 1972. The patient catchment area growth is shown in Figure 1. Total patient contacts are assumed to be greater in March than in May, 1973 because patient demand is generally greater in the winter months and one office day is lost in May (Memorial Day).

In addition to the general increase in patient load from the immediate area of the satellite, the satellite unit is serving patients from a larger geographic area. During a four-week period in May-June, 1973,

associated with the satellite are easier to estimate.

Income generated from office visits at the satellite practice is an estimate of the total marginal income resulting from the satellite. During four weeks in May-June, 1973, a total of \$1182 in charges (expected income) were generated by 118 office visits at the satellite office. The fixed costs, including physician and MEDEX travel, and expected charges are presented in Table 4. Approximately \$799 per month is generated to cover the salaries of the MEDEX and the physicians who are in the practice three days per week as well as additional supplies, bookkeeping, accounting, and other business expenses. If the non-salary business expenses are small and the MEDEX salary and overhead is estimated to be \$12,000 per year,¹ then the physician's earning rate be related directly to the volume of patient visits in the satellite. This relationship, illustrated in Table 5, indicates that the 1973 patient volume of 11 visits per day is not sufficient to cover

TABLE 3

PATIENT OFFICE VISITS AT SATELLITE OFFICE BY TOWN RANKED BY DISTANCE FROM THE SATELLITE (May-June 1973)					
Distance From Satellite Office	Community	Population	Estimated Annual Satellite Office Visits per 1000 Population	Estimated Annual Main Office & E.R. Visits per 1000 Population	
0	Satellite Town	2,276	274.2	68.6	
4	Town 1	789	148.3	65.9	
5	Town 2	6,622	41.2	2.0	
11	Town 3	1,058	24.6	307.2	
12	Town 4	1,587	155.6	8.2	
15	Town 5	525	74.3	445.7	
15	Town 6	1,803	21.6	144.0	
18	Main Practice Town	3,807	13.7	573.6	
24	Town 7	1,922	0	324.7	
25	Town 8	837	0	450.4	
27	Town 9	909	0	657.9	

TABLE 4

MONTHLY BALANCE SHEET FOR THE SATELLITE		
Expected Income (Charges)		\$1,182
Fixed Cost		
Rent	\$100	
Telephone	35	
Receptionist	200	
Mileage	48	
	\$383	
Charges Less Fixed Cost		\$ 799

TABLE 5

PHYSICIAN INCOME AS A FUNCTION OF PATIENT VOLUME ASSUMING AN ANNUAL SALARY AND OVERHEAD OF \$12,000 FOR A MEDEX				
Average Daily Patient Volume	Expected Income Per Year	Overhead Per Year	MEDEX Cost Per Year (½ Annual Salary)	Physician Annual Income (3 Days Per Week)
8	\$12,480	\$4,596	\$6,000	\$ 1,884
11	17,160	4,596	6,000	6,564
15	23,400	4,596	6,000	12,804
20	31,200	4,596	6,000	20,604

a typical family practitioner salary. Fifteen-twenty office visits daily would yield a more representative physician income given that there is additional income from hospital visits and office hours in the main practice. In time, the patient volume may reach these levels.

If care in the satellite had been given by only physicians, an estimated 9.4 patients per day would be required to yield a \$20,000 annual income rate.

The satellite medical practice is an effective method of improving the distribution of primary care services in rural communities with benefits for consumers and providers of health services. For the satellite studied, the impact as measured in annual visits per 1000 population is seen within three months in the community where the satellite is located and within six months in surrounding towns. The fixed monthly cost of the satellite unit is about \$400. After eight months of operation the patient volume has reached 11 visits per day, which is not adequate to cover the salaries of both the MEDEX and physician with the 1973 charge struc-

ture. Office visits at the primary practice location and hospital visits by patients from the satellite region may supplement these revenue estimates. The satellite practice has affected the delivery of ambulatory health care in communities up to 12 miles away. Satellite practices are one reasonable strategy for improving the delivery of health services in contemporary rural American communities.

EPILOGUE

Realizing the necessity for assuring the financial viability of the satellite practice, the providers made two changes in their practice after this study was completed in June, 1973. Fees were increased due to general rising costs and more diagnostic procedures are performed within the practice settings (instead of in other facilities). For a four-week period in July, 1974 the patient volume in the satellite was one greater than for the May-June, 1973 period. However, the total fees generated in the satellite during July, 1974 were 50% greater than for the 1973 period.

ACKNOWLEDGEMENTS

This research was supported at the Department of Community Medicine, Dartmouth Medical School by the National Center for Health Services Research and Development (R18H-500568-01). The efforts by the providers who recorded the Patient Contact Record information used in this study and the suggestions of A.R. Jacobs, M.D. are gratefully acknowledged.

Continued on Page 349

Special Article

Poison Control Center

FRANK H. LAWRENCE, M.D.

In April of 1974, the Maine Medical Center Emergency Department assumed responsibility of the Poison Control Center for the State of Maine. Initial grants from the Department of Health and Welfare and the Area Health Education Center enabled the Maine Medical Center to provide part-time staffing. A grant of \$5000 from the Maine Medical Association facilitated expansion of staffing and improvement of resources. Any patient, employer, physician or nurse can call the Center regarding an ingestion, inhalation or cutaneous contact with a poison and can receive consultation from a physician backed-up with an extensive library of toxicological literature. Optimal service is provided when the Poison Control Center secretary is on duty, currently from 8:30 A.M. to 8:00 P.M., weekdays.

In the period January 1, 1976 to June 10, 1976, the Center received 263 calls; a breakdown of these calls appears below. With the recent inclusion of the Center's number in the telephone book, along with other public service numbers, the public has become more aware of the availability of the service. The Center is in the process of mailing information on poisonous plants to all of the health facilities in Maine in a further effort to educate and make the availability of the service known. Also underway is an investigation of treatment procedures for Paralytic Shellfish Poisoning ("Red Tide Disease") and developing an early-warning information system for hospitals in conjunction with the Department of Marine Resources.

CALLS RECEIVED BY THE POISON CONTROL CENTER JANUARY 1, 1976 — JUNE 10, 1976

Total number of calls	263
% Medical Personnel (patients)	33%
% Non-Medical Personnel (patients)	67%
Advised treatment	27%
(a) Induced emesis with Ipecac	77%
(b) Absorption with Activated Charcoal	23%
Advised to go to a hospital or already calling from a facility	23%
Reassured — no specific treatment	54%

BREAKDOWN OF CALLS BY AGE

0-1	5%
1-5	69%
5-10	1%
10-20	4%
20-30	2%
30-40	3%
40-60	2%
Older than 60	1%
Unknown	12%
Animals	1%

BREAKDOWN OF CALLS BY TYPE OF POISONING

Ingestion	87%
Skin Contact	10%
Inhalation	3%

BREAKDOWN OF CALLS BY PRODUCT

I. Medications	31%
A. Prescriptions	25%
1. Tranquilizers	19%
2. Anti-Depressants	5%
3. Analgesics	19%
4. Sedatives	19%
5. Other	38%
B. Non-Prescription	75%
1. Vitamins	8%
2. Vitamins with Fluoride & Fluoride Pills	16%
3. Vitamins with Iron & Iron Pills	3%
4. Aspirin	16%
5. Cough & Cold Remedies	10%
6. Rubbing Alcohol, Ointments, Liniments	20%
7. Other	27%
II. Plants	9%
A. Poisonous	54%
1. Indoor	54%
2. Outdoor	46%
B. Non-Poisonous	46%
1. Indoor	73%
2. Outdoor	27%
III. Household Cleaning Agents	15%
A. Bleach	5%
B. Cleansers	59%
C. Deodorants	3%
D. Dish Soaps	5%
E. Laundry Soaps	5%
F. Floor & Furniture Polish/Strippers	10%
G. Toilet Cleaners	13%
IV. Cosmetics	12%
A. Perfumes & Aftershaves	50%
B. Creams & Lotions	7%
C. Bubble Bath	10%
D. Shampoos	20%
E. Nail Polish & Removers	13%
F. Deodorants	0%
G. Hair Color	0%
H. Lipstick	0%
V. Household Products & Garage Items	32%
A. Adhesives	10%
B. Ink, Chalks, Crayons	11%
C. Paints	2%
D. Paint Thinner & Strippers	11%
E. Gasoline, Kerosene	1%
F. Insecticides, Pesticides, Mothballs	18%
G. Other Petroleum Products	14%
H. Plant Food	5%
I. Mercury (Thermometers, Thermos)	5%
J. Other Household Items	23%
VI. Spoiled Foods	1%

Maine Medical Center, Portland, Maine 04102

REGIONAL PLASTIC SURGEONS

To the Editor:

At a time when federal agencies and hospitals are especially concerned with definitions, privileges, and capabilities, it behooves an enlightened medical profession to reflect on who's who in the growing field of plastic surgery. We tend to rely on semantics and impressions. If plastic surgery is needed, we may turn to a plastic surgeon because he is a specialist. That tendency is fine, but in following it, we fail to recognize the many practitioners of plastic surgery who do not use the title "plastic surgeon."

Basically, plastic surgery is both a method and a medical specialty. In effect, the plastic surgeon is a specialist in the method. He is obviously a practitioner of plastic surgery, is certified by the American Board of Plastic Surgery, and is officially designated a plastic surgeon. There is virtually no chance of anyone misunderstanding his scope of medical practice.

Who, then, are the other practitioners of plastic surgery? They are specialists in a particular region or organ of the body, for example, ophthalmologists, who after certification by the medical board in their specialty, subspecialize in plastic and reconstructive surgery. Thus, during their specialty training, they master both the specialty region and the method of ophthalmic plastic surgery. Some of these specialists have become known as regional plastic surgeons.

Unlike general plastic surgeons, regional plastic surgeons do not present a consistent identity pattern. Some otolaryngologists may practice under the title "head and neck plastic surgeon" or "cosmetic facial surgeon." Other regional specialists may add the term "plastic surgeon" to their specialty title, for example, the ophthalmic plastic surgeon and the dermatologic plastic surgeon. Still others, such as orthopedists, obstetrician-gynecologists, urologists, neurosurgeons, colon and rectal surgeons, and general surgeons, do not usually add the term "plastic" to their specialty title, although they may use plastic and reconstructive surgical techniques.

A leading ophthalmic plastic surgeon esti-

mates that 1,000 ophthalmologists do a significant amount of plastic and reconstructive surgery. The chief of one otolaryngology residency training program estimates that 4,000 otolaryngologists perform regional plastic and reconstructive surgery. A prominent dermatologist estimates that 300 members of his specialty practice plastic surgery.

About 180 maxillofacial surgeons spend all their time doing plastic and reconstructive surgery. Virtually all of the neurosurgeons, estimated at 2,000 perform cranio-plasties for skull defects. Most of the 9,200 orthopedists practice plastic and reconstructive surgery, because that in the broadest sense is the nature of their work. Many of the 6,000 urologists do some plastic reconstructive surgery in their specialty area, as do many of the 30,000 general surgeons who apply plastic techniques in repairing hernias, strengthening the abdominal wall, removing tumors and ulcers, working with or operating burn units and repairing defects with skin grafts.

Conservative estimates from the most pertinent medical specialties suggest that about 22,000 American physicians practice regional plastic surgery. Of that total, more than 7,000 perform plastic and reconstructive surgery in the head and neck area alone. The significance of these numbers is seen when they are compared with the number of specialists, an estimated 1,500, who are designated plastic surgeons.

Obviously, no medical specialty has the exclusive capability to perform plastic and reconstructive surgery. No board certification by any specialty and no medical title can guarantee a fine surgical result. In discussing plastic surgery with our patients, we might well remember that there are good, fair, and poor surgeons in all specialties. The most important consideration, therefore, is not the surgeon's title but his ability as manifested by his results.

Trent W. Smith, MD
Columbus, Ohio

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THE ROLE OF RURAL SATELLITE PRACTICES IN PRIMARY CARE - Continued from Page 347

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Maine Blue Cross and Blue Shield News

HEALTH COSTS ARE A CO-RESPONSIBILITY

Our "co-responsibility" program is predicated on the assumption that Maine people want more health and benefit information *and can use it*.

If they can use our program, we are further assuming that through Maine consumers taking more responsibility for their own health, demand for services will diminish and the need for further expansion of health services will lessen.

To date, we have sent special newsletters to groups explaining health costs, what we are doing about them and what the individual can do, along with an offer to provide health cost brochures containing essentially the same information for their employees.

Subscriber's Role

The bottom line of our brochure is a plea for subscriber participation. The last section, addressed to the individual, reads as follows: "*what you can do*":

"The cost of care, as we have shown, relates directly to consumer demand. We ask you to follow the advice of your physician, pay heed to the health messages we provide, and to tailor your lifestyle to a regimen of good health.

"Medical technology will continue to grow and be of benefit to all of us, but if each of us takes the responsibility for our own good health, making sure that we have done everything possible to keep our bodies in good working order, we can reduce the demand on the system, and begin to control health care costs.

"We can continue to have high expectations of the medical system only if we have equally high expectations for our own living habits."

If you would like a copy of the brochure, write: Communications Department, Maine Blue Cross and Blue Shield, 110 Free Street, Portland, Maine 04101.

Maine Blue Cross and Blue Shield's Role

To back up the individual's effort to take more responsibility for his own health, we are sponsoring "Housecall" and "Update on Health," televised health information featuring Timothy Johnson, M.D. of Harvard Medical School. "Housecall" is a half-hour program and airs once weekly, while "Update" is a 1½ minute health news brief and appears 3 times a week. We have also provided a grant to WCBB, a local public television station, to produce "Maine Medical Call," a dial-in health information program.

We will also soon be offering "Tel-Med," a dial-in system through which a caller can request to hear a tape on a particular health subject. We also have our usual library of BCA and NABSP booklets available.

We have developed a stuffer for use by employers which promotes the Dr. Johnson series and our booklets. If there is employer demand for further health education help, we may consider providing "Housecall" tapes and other services for their use.

Necrologies

BERTRAND A. BELIVEAU, M.D.

1909-1976

Dr. Bertrand A. Beliveau, 67, of Lewiston, Maine, died on July 15 at St. Mary's General Hospital following a short illness.

Born in Lewiston on October 7, 1909, he was the son of Emerilde and Claudia Beliveau.

Dr. Beliveau was graduated from Lewiston High School and Georgetown University and received his medical degree from Georgetown University School of Medicine in 1934. He interned at St. Mary's General Hospital and had specialized in Internal Medicine in Lewiston since 1934.

He was a former physician for the City of Lewiston, chief of medicine and former president of the medical staff at St. Mary's General Hospital and on the courtesy staff at the Central Maine

General Hospital. During World War II, he served as a Major in the U.S. Army Medical Corps with the 67th Medical Corps in England.

Dr. Beliveau was a member of the Androscoggin County Medical Society, the Maine Medical Association, the American Medical Association and the American Association of Internal Medicine.

Surviving are his widow, the former Rita Fortier; two daughters, Mrs. John Thomas of Wayzata, Minnesota and Mrs. Edward Dick of Tucson, Arizona; one son, Attorney John B. Beliveau of Lewiston; one brother, Albert Beliveau of Lewiston; and eight grandchildren.

JOHN T. KONECKI, M.D.

1916-1976

Dr. John T. Konecki, 60, of West Auburn, Maine, died unexpectedly August 30 at the St. Mary's General Hospital in Lewiston, Maine. Dr. Konecki, chief of radiology at the hospital, had been on duty and was preparing to leave for home at the time.

He was born in South Portland, Maine on February 17, 1916, the son of Zigmont and Katherine Konecki.

A graduate of Bowdoin College in 1939, Dr. Konecki received his medical degree from Boston University School of Medicine in 1943. He interned at the Maine General Hospital and served residencies in radiology at the Cushing V.A. Hospital in Framingham, Massachusetts, the Boston V.A. Hospital, the West Roxbury V.A. Hospital and Children's Hospital in Boston. Dr. Konecki practiced in Portland, Maine and in Cambridge, Massachusetts, locating in Lewiston in 1953.

In World War II, he served in England in the U.S. Army Medical Corps, holding the rank of Lieutenant Colonel, and retired with the rank of Colonel from the 1125th U.S. Army Hospital, U.S. Army Reserves. For years, Dr. Konecki was

Commander of the Army hospital unit in Auburn, and was also active in the Association of Retired Officers.

Dr. Konecki was a member of the Androscoggin County Medical Society, the Maine Medical Association, a fellow of the American College of Radiology and served as an officer on the board of directors and on the executive committee of the College. He was also consulting radiologist at the Central Maine General Hospital, Pineland Hospital and Training Center, Bridgton Hospital and the Augusta General Hospital.

He married Ruth Nihan of Lynn, Massachusetts, who survives.

Other survivors include three daughters, Mrs. James Wellehan of Auburn, Mrs. Thomas E. Delahanty, II of Lewiston and Miss Nancy Konecki of Auburn; two sons, John Thomas, Jr. of Orono, Maine and Thomas John of Auburn; a sister, Mrs. Lottie Sweirzinski of South Portland, Maine; a brother, Leon of Tacoma, Washington; and five grandsons.

ROBERT M. MORRISON, M.D.

1930-1976

Dr. Robert M. Morrison, 45, of Cape Elizabeth, Maine, a Portland, Maine gynecologist and obstetrician since 1962, died on September 8 in a Portland hospital after a long illness.

Born in Portland on September 13, 1930, he was the son of Elizabeth J. and James Morrison.

He attended Portland schools and was a graduate of Deering High School, Bowdoin College in 1952 and received his medical degree from McGill University Faculty of Medicine in 1956. Dr. Morrison interned at the Maine Medical Center and served a residency in obstetrics and gynecology at the Boston City Hospital. He served in the U.S. Air Force Medical Corps at Holloman

AFB in New Mexico from 1960 to 1962, holding the rank of Captain.

Dr. Morrison was a member of the Cumberland County Medical Society, the Maine Medical Association and the American College of Obstetricians and Gynecologists. He was also on the staffs of the Maine Medical Center and Mercy Hospital.

Besides his parents, he is survived by his widow, the former Beverly Withee; a son, Brett Carter Morrison and three daughters, Susan Annette, Tracy Lynn and Dina Lea Morrison, all of Cape Elizabeth.

News, Notes and Announcements

Central Maine General Hospital
and
St. Mary's General Hospital
announce

"Clinical Problems in Medicine and Surgery" A Regional Postgraduate Course

- Jan. 26, 1977 COMMON NUTRITIONAL PROBLEMS
Drs. Mark E. Molitch and Thomas E. O'Donnell
- Feb. 23, 1977 THE MANAGEMENT OF PEDIATRIC EMERGENCIES
Drs. Joseph L. Kennedy, Jr. and Richard D. Kenney
- March 23, 1977 OVERVIEW OF DEPRESSION
Dr. Stephen B. Bernstein
- April 27, 1977 CORONARY ARTERY DISEASE: THE MEDICAL-SURGICAL CONSIDERATIONS
Drs. John S. Banas and Richard J. Cleveland
- May 25, 1977 CLINICAL PROBLEMS IN INFECTIOUS DISEASE
Dr. Michael Barza
- June 15, 1977 ONCOLOGY — HEMATOLOGY
Dr. Richard A. Rudders

TIME: 1:30 to 5:00 p.m. Wednesdays

PLACE: Thompson Auditorium, Central Maine General Hospital, Lewiston, Maine

REGISTRATION FEE: \$15.00 per session. Residents and medical students, no fee. This program is supported in part by Area Health Center funds.

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First International Glaucoma Congress

The world's leading medical authorities on glaucoma will lecture on their latest research findings at the First International Glaucoma Congress, January 31-February 1, 1977, at the Diplomat Hotel, Hollywood, Florida. The glaucoma congress is being held in conjunction with the 12th Annual Scientific Assembly of the American Society of Contemporary Ophthalmology January 30 through February 5 at the same site. The Congress is sponsored by Lederle Laboratories.

The glaucoma congress will be under the honorary chairmanship of Dr. Bernard Becker, of Washington University, St. Louis, recognized as a pioneer in glaucoma research. Authorities in other areas of ophthalmic research are scheduled to conduct seminars during the week-long meeting: Cornea-External Diseases, Dr. Claes Dohlman, Harvard Medical School; Cataract, Dr. David Paton, Baylor University Medical School; Vitreous-Choroid-Retina, Dr. Harvey Lincoff, Cornell University Medical School; and Oculoplastic Surgery, Dr. Pierre Guibor, Doctors Hospital, New York, N.Y.

A series of tutorials and workshops will be offered in Microsurgery, Phakoemulsification, Oculoplastic Surgery, Vitrectomy, Fluorescein Angiography, Gonioscopy, Ultrasonic Evaluation of the Eye, External Ocular Disease, Intraocular Lens Technology, and Malpractice. The program meets the criteria for 42 hours of credit in Category I for the Physician's Recognition Award of the American Medical Association and for

the ASCO Certificate of Advanced Studies in Ophthalmology.
For further information: Dr. John Bellows, Director, ASCO, 6
North Michigan Avenue, Chicago, Illinois 60602.

Seventh Annual Aspen Radiology Conference

The Seventh Annual Aspen Radiology Conference, designed for physicians and scientists interested in diagnostic radiology, nuclear radiology and diagnostic ultrasound, will explore the impact of clinical and technological advances on radiologic practice.

The Conference will be held February 28 to March 4, 1977 with registration Sunday, February 27 at the Aspen Institute for Humanistic Studies, Aspen, Colorado.

The topics for discussions will include advances in bone, cardiovascular, gastrointestinal, ob/gyn and neuroradiology involving a tri-radiological approach. The advances in the 3 radiological subdivisions relating to these topics will be surveyed as refresher courses in independent diagnostic radiology, nuclear radiology and diagnostic ultrasound sessions. Instructive cases, illustrating these subjects and previewed by the Conference, will be presented for open discussion in the afternoons.

Significant changes programmed for the 1977 meeting include an independent course in diagnostic ultrasound and a plenary session on total body CT scanning, comparing this modality with diagnostic ultrasound and nuclear imaging. The Conference has been extended from 4 to 5 days.

The 1977 Conference will not offer a course in radiation oncology.

Further information may be obtained from Emanuel Salzman, M.D., Conference Chairman, Division of Radiology, Beth Israel Hospital, Denver, Colorado 80204 (303) 825-2190.

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CHAMPUS — Change in Prevailing Screens

In accordance with a directive from the Department of Defense, CHAMPUS payments, beginning with claims processed on or after July 1, 1976, will be based on calendar year 1975 charge information.

Each physician's customary charge will be determined from charge information on regular Blue Shield claims processed in 1975 and charge data submitted directly to us in 1975. The 75th percentile of all of these customary charges will be the maximum allowances. Charges shown on claims received will be compared against both the physician's 1975 customary charge and the 75th percentile, and the smaller of these three amounts will be paid.

Meetings of the State of Maine Chapter

American Academy of Family Physicians

The Fall meeting of the State of Maine Chapter of the American Academy of Family Physicians was held Saturday, September 11, 1976 at the Houlton Regional Hospital at Houlton with the President, John J. Pearson, M.D., presiding.

The clinical program theme "Management of Hypertension" was under the direction of Edward Williams, M.D. of Houlton. The two visiting speakers were Harry Gavros, M.D., Professor of Medicine at Boston University School of Medicine and William Chapman, M.D., Dept. of Medicine, Peter Bent Brigham Hospital, Boston. This symposium was followed by a panel discussion moderated by John B. Madigan, M.D. of Houlton and consisting, in addition to the speakers, of G. I. Wilson, M.D. of Houlton and Hans Epstein, M.D. of Woodstock, New Brunswick, Canada.

During the luncheon interval, a general discussion was opened regarding phasing out of the Bangor Mental Health Institution, formerly known as the Bangor State Hospital for the insane. It

was the unanimous opinion of all the physicians present that the question of closing the institution has been relegated to a task force of laymen and devoid of any physician participation. It was further unanimous that the Bangor State Hospital was worthless to us as physicians as a part of our armamentarium in caring for our patients needing institution care. For this reason, it was brought out that the closure of BMHI made no difference to the physicians of the State.

At the close of the assembly, a directors' meeting was held. At this meeting, it was voted to inform the Governor of the State by open letter that the Maine Chapter of AAFP express the distaste of the present policy of BMHI, and secondly, to point out that no medical opinion has been solicited.

At the convocation and inaugural ceremony held during the Annual Scientific Assembly of the American Academy of Family Physicians, (at Boston, Mass. Tuesday, September 21, 1976) 1,400 physicians of the United States, the U.S. possessions and Canada, were conferred the degree of Fellow in the AAFP. (It was pointed out that this medical organization is the second largest in the country, second only to the American Medical Association.)

Among those receiving the fellowship award at the fitting ceremony at the Hynes Memorial Auditorium were the following members of the Maine Chapter: Drs. Daniel F. Hanley, Brunswick; Karl V. Larson, East Machias; Harold N. Burnham, Gorham; Edward P. Williams, Houlton; Joseph T. DeGrinney, Livermore Falls; Felix M. Garcia-Rey, Milo; John M. Bischoffberger, Naples; Harland G. Turner, Norridgewock; John J. Pearson, Old Town; Gretl J. Hoch, Phillips; Donald A. DeCosta and E. Stanley Young, Poland Spring; Robert E. Caven, Charles R. Geer and Giovanni Mazzone, Portland; and Anthony L. D'Andrea, South Portland.

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County Society Notes

Androscoggin

The meeting of the Androscoggin County Medical Society was held at Steckino's Restaurant in Lewiston, Maine on Thursday, September 16, 1976.

The meeting was opened by the President, Dr. Stanley D. Rosenblatt, at 8:15 p.m., with 32 members and 4 guests present.

First item of business was report of audit by Earl Austin. At the end of December 1975, the balance was \$3,125.98. There were no discrepancies and the Androscoggin County Medical Society appeared to be in honest and capable hands.

Communication from Dr. Hanley indicated that Dr. Cyprien L. Martel, Jr. had been appointed to fill the unexpired term of counselor vacated by the resignation of Dr. Richard M. Swengel.

Dr. Thomas F. Shields reported on a preliminary recommendation of the Legislative Malpractice Committee and Dr. Rosenblatt appointed a committee chaired by Dr. Shields to work with this committee. The other members were Drs. Rosenblatt, Swengel, Martel, Donald Anderson and Charles Hannigan.

Applications of Drs. Frederick C. Holler and Michael T. Drouin were approved and voted into the membership.

The Society will not participate in this year's diabetic week.

Approved as Affiliate members for 1977: Drs. Merton N. Flanders, Mahlon R. Mason, Wedgwood P. Webber, Ralph Zanca and William Spear, recently retired. The status of Dr. Jan Knoppers has not been cleared and should be deleted from the roll of Junior member.

There was a report by Mr. Chris Boys on the swine flu program and he and Marty Bernstein were guests. They are coordinators for the program at Central Maine Medical Center and St. Mary's General Hospital. The county and State societies have gone on record as wishing to cooperate with this program which probably will start in about three weeks. It will start in Portland and work its way through the large population centers north.

Mr. John Wall then presented the reasons for the Emergency

Call Service 911. He brought out that the telephone company is anxious to have this particular number since automation of telephone equipment will soon eliminate most of the telephone operators in the State. There was much discussion regarding feasibility of this. Presently this applies to our small communities.

Dr. Alan Hume talked on Emergency Medical Services and indicated that he has been here since October and has been speaking to numerous county societies and feels that any program must be tailored to the individual needs of the community and the medical societies must be utilized with their members as resource people in these different areas.

Meeting adjourned at 9:30 p.m.

CHARLES A. HANNIGAN, M.D., *Secretary pro tem*

Franklin

The Franklin County Medical Society met on September 7, 1976.

Further discussion of home deliveries and appropriate resolution of the questions regarding them occurred. Dr. William T. Yates reported that the American College of Obstetrics and Gynecology had a policy opposed. Dr. Onion reported that the matter had been turned over to the Maine Medical Association's Dr. Hanley and the State Committee for Maternal Health and Child Welfare.

Discussion of the benefits and responsibilities of County and State Society membership presented to the several new physician members of the hospital staff. Dr. Daniel Barnett expressed immediate interest in joining the County and State Society. Others will consider it and report back at the next meeting, and Dr. Barnett's application will be acted upon at that time.

DANIEL K. ONION, M.D., *Secretary*

Letters to the Editor

To the Editor:

In a letter dated May 4, 1976, I asked the help of State medical societies in advising their membership of the legal consequences of rebate arrangements with clinical laboratories in the Medicare program. I am grateful that many of you included that information in your routine newsletters. I am writing once again to ask that you consider bringing another matter to the attention of your membership. This relates to claims for Medicare reimbursement for laboratory services.

Medicare reimbursement rules require that the reasonable charge for a laboratory test that was performed by an independent laboratory, but billed by the attending physician, be related to the cost the physician incurred in obtaining the service for his patient. The Medicare carriers are permitted to allow as reasonable a nominal charge by the physician for the drawing of specimens and handling expenses. However, charges representing merely a physician markup of the charges over and above that actually imposed by an independent laboratory for the test itself are improper. Moreover, an independent laboratory not certified to perform a given test under Medicare may not be reimbursed with Medicare funds even though that test is billed through a physician.

In carrying out their responsibilities, Medicare carriers are required to determine the source of the lab service when the source is not indicated on the physician's bill. Where the service was performed by an independent lab, the carrier must determine that the laboratory is certified by Medicare to perform such tests and the appropriate payment to cover the laboratory's customary charge, rather than the physician's.

Review of Medicare claims indicate that some physicians con-

tinue to submit bills for lab tests without showing that the services were actually performed by independent laboratories. We think that it is essential that all of your members are apprised of and understand Medicare requirements, and that there be full disclosure by a physician concerning the source of tests for which payment is claimed under the program. Our aim is to avoid the possibility of physician billing in a manner that could have serious legal consequences.

If you would like us to assist in the preparation of informational materials on this subject, or if you have any questions, please do not hesitate to contact us.

THOMAS M. TIERNEY
Director
Bureau of Health Insurance
Dept. of Health, Education, and Welfare
Social Security Administration
Baltimore, Maryland 21235

To the Editor:

I am interested in finding the incidence of allergic reactions to chocolate because of a recent query I received from a chocolate manufacturer.

I would appreciate hearing from physicians the estimated number of their patients allergic to chocolate, and the symptoms produced. I would also appreciate receiving specific case reports, results of laboratory tests, and any other comments on the subject.

CLAUDE A. FRAZIER, M.D., P.A.
Doctors Park, Bldg. 4
Ashville, N.C. 28801



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Toward an Early Diagnosis of Carcinoma of the Colon

JOHN J. MCDEVITT, IV, M.D.*

ABSTRACT

Carcinoma of the colon and rectum occurs with greater frequency than any other malignancy in Maine. The survival rate has remained around 40 percent since 1950 in the United States. Early diagnosis, especially in the asymptomatic stage is often equivalent to localized disease which has a survival rate of 80 to 90 percent. A diagnostic schema is presented which may not only result in early diagnosis but even perhaps prevention of colon and rectal carcinoma. Factors affecting when the schema should be undertaken in various patient populations are discussed.

In Maine, cancer of the colon or rectum (hereafter called colon cancer) has the highest incidence of any carcinoma. There are six hundred new cases diagnosed each year with three hundred deaths annually. The comparable figures for the United States are 99,000 new cases and 49,000 deaths.¹ In the twenty years since 1950, five-year survival has remained essentially unchanged at from 37 to 44 percent.² In contrast to many neoplasms, colon cancer can now be detected early, often even when asymptomatic. Lack of symptoms frequently bespeaks localized disease with a cure rate of 80 to 90 percent versus a 14 percent rate in disseminated disease.^{3,4} With this in mind, many diagnostic schema have been developed.^{5,6} That suggested by Winawer is shown in Figure 1.⁶ Once begun, the schema is followed to its conclusion, however, the time at which it is instituted will depend on the patient's age and other risk factors to be discussed.

THE DIAGNOSTIC TOOLS

Occult Blood — The diagnostic value of testing

the stool for occult blood by using guaiac-impregnated paper (Hemoccult® — Smith, Kline, & French Diagnostics, Philadelphia, Pa.) has been shown.³ For maximal yield the patient must:

- 1) Eat a high residue diet (fruits, vegetables, peanuts, popcorn, "All Bran"®) for the forty-eight hours prior to the test hopefully to cause abnormal areas to bleed.
- 2) Eat no meat for the twenty-four hours before the procedure to reduce the rate of false-positives.
- 3) Place a sample from two different portions of the same stool on each of two Hemoccult slides. This is repeated on three consecutive daily evacuations for a total of six slides.
- 4) Forward slides promptly to the physician since there may be an increased rate of false-negatives with delay.

In a study of more than six thousand asymptomatic patients, one percent had positive slides. Usually only one or two slides were positive thus implying that "spot checking" a rectal specimen is insufficient. In the fifty-four patients with positive stools who were investigated, there were sixty-three polyps and five cancers.⁷ Of note is that positives cannot be discounted merely as "hemorrhoids" and any degree of positivity requires further investigation. The cost of this simple test is about \$1.12.

Digital Exam — In the past, it was thought that one-half of all rectal cancers were within reach of the examining finger, i.e., within six cm. of the anus. Now we know that only 12 percent are palpable on digital exam, but this is still a respectable argument for the test.⁸ Unfortunately, one study showed that only 50 to 60 percent of physicians perform a rectal exam on asymptomatic patients.⁹

Sigmoidoscopy — Symptomatic patients or those with certain risk factors to be discussed later should have routine annual sigmoidoscopy. Its use annual-

*Section of Gastroenterology, Medical Service, Eastern Maine Medical Center, Bangor, Maine 04401.

SCREENING FOR COLORECTAL CANCER

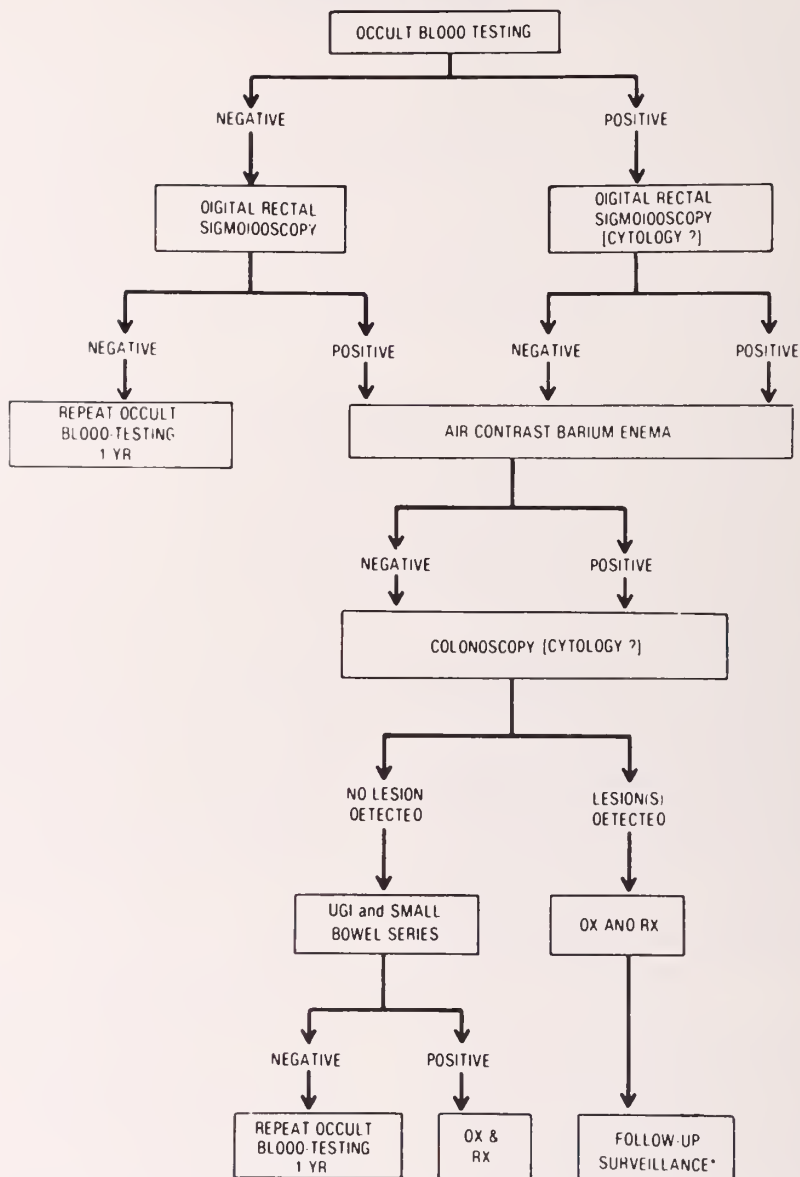


Fig. 1. The above schema has been suggested by Winawer, et al for screening all of those who are symptomatic as well as those who are asymptomatic but at high risk. See Table 1.

ly in asymptomatic patients is controversial, however, if performed on this basis, it has been shown to not only provide early diagnosis but also markedly reduce the anticipated incidence of rectal cancer.¹⁰ This may very well be because all lesions, even benign polyps, were removed at the time of each procedure. In addition, sigmoidoscopy at longer intervals such as every two to three years should detect any cancers while they are still localized.¹⁰ As a result of these findings, there appears to be a resurgence of interest in sigmoidoscopy as a routine diagnostic tool in the asymptomatic patient on a regular basis every one to two years.^{5,11}

Barium Enema — Ten to twenty percent of colon cancers are missed on the initial barium enema

largely because they are mistaken for feces.^{11,12} This pitfall is clearly demonstrated in Figure 2 in which a cecal carcinoma was visualized colonoscopically after a barium enema in a poorly prepared patient was read at another hospital as being normal. The key is in the preparation. The preparation which we have found to be satisfactory is as follows: On the day prior to the procedure, the patient ingests a clear liquid diet, drinks one bottle of Magnesium Citrate at noon, has two Dulcolax® tablets at 5 p.m., and drinks at least one eight-ounce glass of fluid hourly for six hours beginning in the early afternoon. A Fleets® enema is used the night before and the morning of the procedure. A commercially available kit, the Evac-Q-Kit® (Warren-Teed Pharmaceuti-



Fig. 2. A 59-year-old male in excellent health except for episodic bleeding per rectum of three weeks' duration. Left, barium enema of cecal area filled with feces but read as normal. Right, photograph through the colonoscope of a greatly magnified adenocarcinoma in the cecum of the same patient. The black dots are due to broken fiber bundles in the colonoscope.

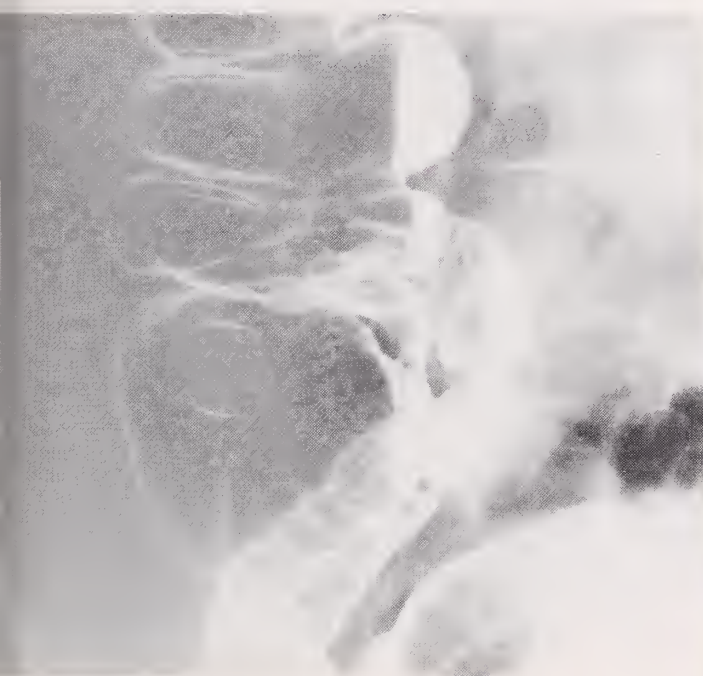


Fig. 3. An example of a good quality air contrast barium enema with detail of cecum. The yield with this study is considerably higher than that of the routine barium enema.

cals, Inc., Columbus, Ohio) has also been found to be safe and useful.¹⁴

Although the adequacy of the preparation is extremely important, a significant number of lesions are missed on routine barium enemas, but this figure (perhaps as high as 40 percent) can be reduced

markedly by using the air contrast technique in which the radiologist instills thick barium and air. The preparation is the same as that for a routine barium enema. The study takes the radiologist perhaps twice as long as a routine barium enema. A good air contrast study with detail of the cecum is



Fig. 4. The colonoscope has been advanced to the cecum. Only about 90 cm. of the instrument is in the bowel despite its having traversed perhaps twice this distance because the bowel has "telescoped" over the instrument. Aside from visual evaluation, biopsy and polyp resection can be performed through the instrument.

shown in Figure 3. By using a technique producing the clarity shown, it would seem impossible to miss a lesion such as that shown in Figure 2.

An air contrast barium enema should be done in any high risk or symptomatic patient. Perhaps in the not too distant future, it will become routine.

Colonoscopy — The entire colon can now be visualized directly by the use of the fibre-optic colonoscope (Figure 4). It permits direct biopsy of lesions and is both therapeutic and diagnostic where polyps are encountered since they can be removed

in their entirety by the instrument for study by the pathologist, an important consideration because there are frequently changes only in portions of the polyp. The risk of polypectomy through the colonoscope is considerably less than at laparotomy.¹⁵ Since there is a suggestion that one-half to two-thirds of cancers arise from previously benign adenomatous or villous polyps, these should be removed and not "followed."¹⁶ In addition to polypectomy, colonoscopy is particularly effective in the evaluation of the postoperative colon and in-

inflammatory bowel disease, two areas in which x-ray is often equivocal. It is important to recognize that colonoscopy and the barium enema are complementary and not competitive. Colonoscopy facilities and qualified personnel are scarce relative to x-ray facilities so that it is unjustified to bypass the air contrast barium enema. Colonoscopy is frequently indicated even if the enema is positive not only to evaluate and verify the presence of the lesion seen on x-ray but also to check for synchronous lesions.

WHO AND WHEN TO TEST

All symptomatic patients should be evaluated using the diagnostic schema just described but what about those without symptoms? An abbreviated list of those conditions which correlate with an increased risk of colon cancer is shown in Table 1.

TABLE 1

Factors Predisposing to Colon Carcinoma

Age over 40
Ulcerative colitis
Granulomatous colitis
Presence of polyps (non-genetic)
Familial polyposis syndromes (genetic)
Previous colon carcinoma or polyps
Family history of colon carcinoma

Patients falling into the categories on this list should be evaluated at an earlier age than the general population, and all those over forty should be studied.

In terms of frequency of physician encounter, those patients with previous colon cancer, family history of colon cancer, polyps or inflammatory bowel disease predominate. Those with previous colon cancer have a three times greater risk of a second bowel carcinoma than the general population. Their relatives are also at increased risk of about the same order of magnitude.

Familial polyposis syndromes are genetic and rare relative to the occurrences of polyps in the general population. Except in the case of the familial variety, a controversy about the relationship between colonic polyps and carcinoma has existed for many years. Even discounting carcinoma in situ and focal atypia, the incidence of malignancy was 6.8 percent in a large series of unselected polyps removed colonoscopically.¹⁵ In addition, there is a suggestion that polyp removal may be prophylactic.¹⁰ Despite this, a majority of polyps are not malignant, however, at least one-half to two-thirds of colon cancers arise from polyps.¹⁶ The increased risk of development of a second intestinal carci-

noma where polyps are found in the resected specimen is considerable.¹⁶ It, therefore, seems prudent to remove polyps when they are found.

Inflammatory bowel disease especially ulcerative colitis is associated with a significant predisposition to colonic carcinoma. In the case of ulcerative colitis, the risk is a function of several factors with duration of illness being very important. A Mayo Clinic study showed that in children there was only a 3 percent incidence of colon carcinoma during the first ten years of the illness, but the risk then became 20 percent per decade thereafter.¹⁷ The monitoring of patient with colitis clearly presents a problem under the schema shown in Figure 1 because little weight can be placed on the presence of blood in the stool. A satisfactory answer to this problem has yet to be found. Our approach is to perform sigmoidoscopy each year and barium enema every second year on patients with ulcerative colitis even if quiescent.

It is hoped that if the risk factors just described are used as the basis for the application of the schema shown in Figure 1, significant improvement in colon-rectal carcinoma survival can be achieved.

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Computed Tomography in Maine:

Initial Clinical Experience

HARRY S. TAMM, M.D.* and JOHN M. LONG, M.D.**

At the Annual Congress of the British Institute of Radiology in April of 1972 a new system of x-ray scanning was announced by Mr. G. M. Hounsfield, a senior research engineer with EMI Limited, and Dr. James Ambrose, Chief of Neuroradiology at the Atkinson Morley's Hospital in London.^{1,2} Never in the history of modern medicine has a diagnostic technique been awaited with such anticipation and accepted with such boundless enthusiasm. In 1973, the first four units were installed in the United States — in Boston, Chicago, Rochester (Minnesota) and Washington (D.C.). In the four years which have subsequently elapsed, over six hundred CT scanners have been manufactured by a dozen different firms and installed throughout the nation.³ The scope of application has been extended from the cranium and orbits to the entire body. The rapid technological advancement in this field has been outstripped only by its spiraling costs. A total sum of over \$250 million has already been spent on CT equipment, a cost that someday will be borne by medical consumers.³ The almost infectious spread of the desire to possess this equipment has led to open controversy as to optimal placement and usage.^{4,5} Many questions must remain unanswered as the technique is still in its infancy. Who can predict what the ultimate cost effectiveness of this equipment, the population required to fully utilize the units and the ultimate effect of CT on current diagnostic modalities will be?

The first computed tomography unit in Maine was placed at the Eastern Maine Medical Center in December 1975. It is an EMI Head Scanner. The situation at EMMC is somewhat unusual in that the scanner unit is owned by a private corporation but placed in the hospital where acutely ill patients, those requiring anesthesia, and out-patients may benefit. Furthermore, day-to-day supervision and interpretation of the examinations is shared jointly by several neurologists and a neuroradiologist. The purpose of this paper is not to present our situation as an ideal solution to various controversies, but to review the early results of our experience, point out applicability and pitfalls, and compare our data with others.

DEFINITION

CT has at this point in time been established as an extremely reliable and safe method for the investi-

gation and precise localization of abnormalities of the brain. The cranium is scanned in successive layers in the axial projection by a very narrow beam of x-rays, in such a manner that the transmitted x-ray photons across a given point can be precisely measured. On our current EMI head scanner with a 160 x 160 element computer matrix, 160 transmission readings are obtained per scanning sequence and at the end of each sequence the system is rotated one degree around the patient's head. This continues for 180 degrees, allowing 28,800 transmission computations per level. The tomographic examination is carried out at six to eight levels, allowing study of the entire cranium. Because of the large number of photon transmissions which are detected, localized and stored, a wide range of tissue densities can be discriminated in a manner previously possibly only by use of a positive (angiography) or negative (pneumography) contrast agent.

Cranial CT has met with such rapid acceptance because it is neither associated with the discomfort nor the potentially permanent neurological sequela of angiography and cranial pneumography, but provides information of equal or greater reliability.^{6,7}

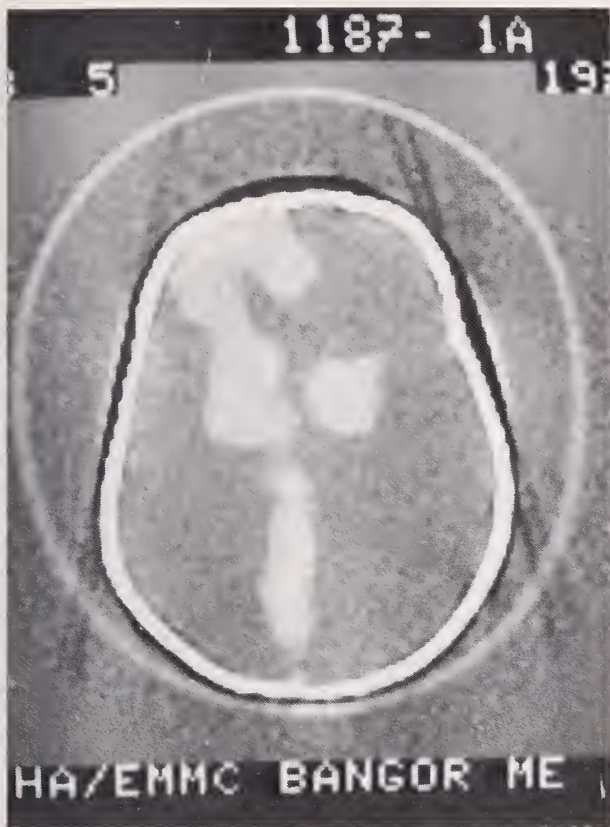
Patients are often referred for this study at a time when their clinical signs and symptoms may not have justified the risk of cerebral angiography or pneumoencephalography. Hence, earlier diagnosis may be established and subsequent definitive treatment may be instituted. As a result of the screening, some patients are referred for additional neuroradiological procedures. For others, hospital admission may be prevented or its duration reduced, and the additional procedures avoided. Provided that CT scanning is available without any significant waiting period, considerable cost savings may accrue.⁸

Patient radiation exposure is another important consideration that must be taken into account whenever a physician considers a diagnostic examination. Measurements have shown that CT scanning of the head subjects the patient to a similar integral radiation dose as a skull series. This is possible because of the tight collimation of the x-ray beam, subjecting only a narrow band of the head to ionizing radiation at a given time.

Newer generations of CT scanners are being introduced with higher resolution and faster scan speed. This is particularly important for the thorax and abdomen where respiratory motion can cause considerable artefact. Scanning times as short as 4 seconds per section are available. The multiple array of detectors and fan beam geometry allowing these improvements result in considerably higher

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**Neuroradiologist, Eastern Maine Medical Center, Bangor, Maine 04401.



HYDRANENCEPHALY

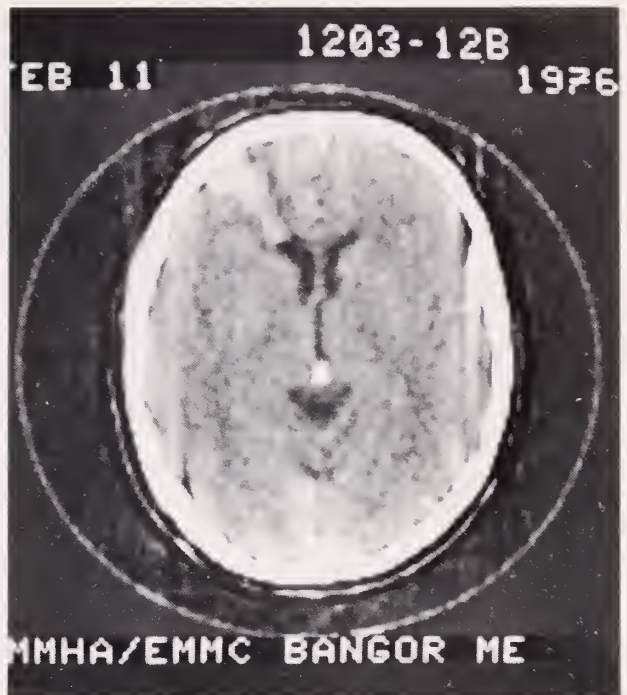
This scan through the hemispheric substance of an infant shows the absence of occipital and parietal brain and the presence of only a small amount of left frontal cortex and basal ganglia. The diagnosis is hydranencephaly.

cost. The higher resolution is the result of higher photon flux. Clearly, this means increased patient radiation exposure which can be as high as 20R per section.⁹ High resolution, i.e., high dose CT scanning must be employed selectively by physicians informed of the indications for the study and aware of the effects of ionizing radiation.

SUBJECTS AND METHOD

All of the scans to be described were performed between December 1975 and March 1976 on our standard "first generation" EMI head unit with water bath reference and the updated 160 x 160 matrix. Three hundred and eleven patients' records have been reviewed. The majority of these patients were referred by neurologists and neurosurgeons in the Bangor area, but some came from as far away as Portland and Houlton. No attempt was made to select the patients by referring diagnosis. The studies reviewed were simply the first ones performed.

Access to all pertinent data from history, neurological examination, x-rays and laboratory information has been important in order to select the correct angulation of the patient's head, determine the need for intravenous contrast "enhancement" with iodine containing drugs, and select the appropriate



ARTERIOVENOUS MALFORMATION

Scan through the level of the frontal horns of the lateral ventricles shows a contrast dense lesion with a small area of surrounding cerebral edema. Angiography confirmed the presence of a left frontal arteriovenous malformation, subsequently removed surgically.

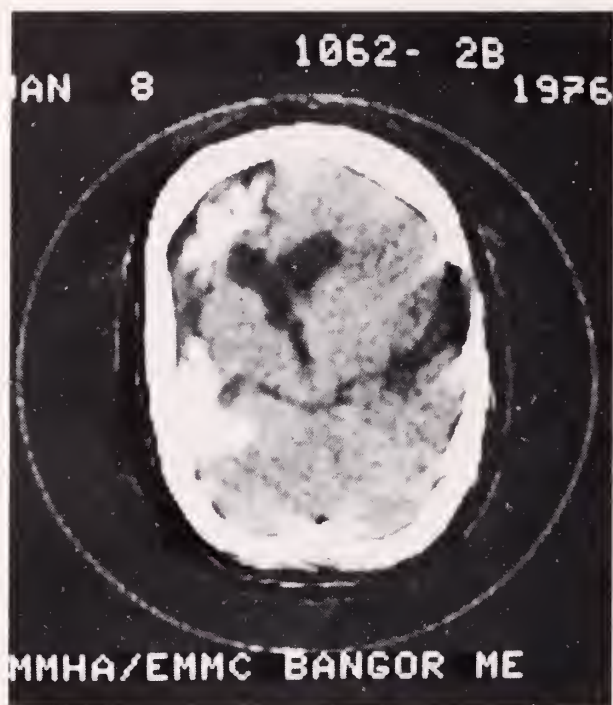
section thickness or the need for overlapping sections.

RESULTS

A total of 311 scans were included in this study. Of these, 170 or 54.7% were performed with contrast enhancement. A total of 14 required some form of sedation and 2 of these required general anesthesia. This represents 4.5% of all of the scans. Only two of the patients had allergic reactions to the contrast material. One of these was a severe laryngospasm requiring intravenous epinephrine.

The total number of abnormal studies was 177 or 56.9%. The scan diagnoses fell into four major categories, with the remainder distributed among 17 others. The most common were infarction, tumor, hydrocephalus and cerebral atrophy. There were 42 infarctions (13.5%). Forty-one were hemispheric, and 1 was in the posterior fossa. Thirty-six tumors were diagnosed, 11.6% of the total. Twenty-six of these were hemispheric, 5 were suprasellar, and 5 were in the posterior fossa. Finally, there was a total of 18 cases (5.8%) of hydrocephalus, and 48 cases (15.4%) of cerebral atrophy.

Excluding the above, the largest additional diagnostic category was postsurgical followup (2.3%). Others included aneurysm, arachnoid cyst formation, cerebral hemorrhage, third ventricular cyst, abnormal intracranial calcifications, cerebral edema, contusion, porencephaly, Sturge-Weber disease, extracerebral hematomas, cerebral hemi-



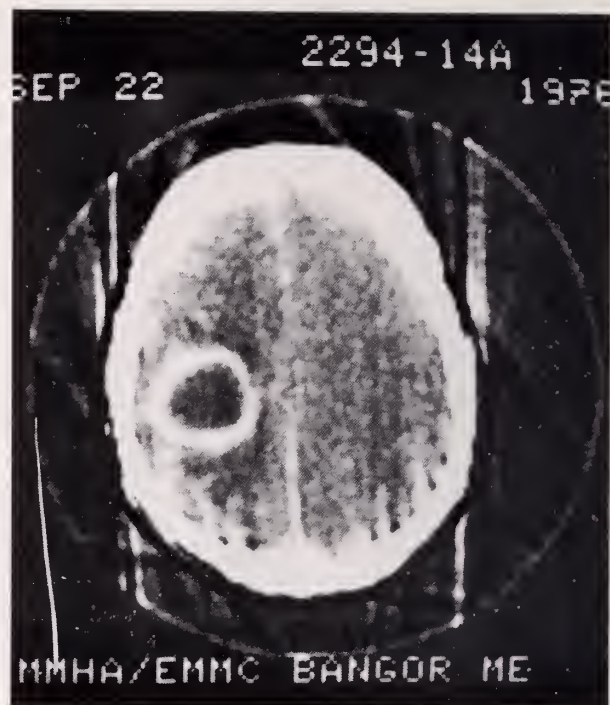
STURGE WEBER SYNDROME

This is the scan performed on a young male with right sided hemiatrophy, seizures, and a left facial "port wine" stain. The study shows well the left cerebral cortical atrophy and calcification. The low density lesion on the right is the sign of previous removal of a brain abscess.

atrophy, hydranencephaly, and cerebral abscess. None of these amounted to any significant percentage of the total.

DISCUSSION

There is no question that computed tomography has become an important diagnostic tool in the evaluation of patients at the Eastern Maine Medical Center. Comparing our initial data to that generated at the Atkinson Morley's Hospital during the time when its machine was first installed, several differences are apparent.¹⁰ The most common diagnosis at EMMC was cerebral cortical atrophy. This diagnosis was made in 15.4% of the cases, while it was made in only 6.3% of the cases in the London study. Although one potential explanation for this is the fact that the 160 x 160 matrix system used at EMMC has a higher resolution than the 80 x 80 matrix used for the initial studies in London, a second and more substantial issue would involve the question of when the diagnosis of cerebral atrophy should be made. In patients over 65, changes of atrophy consistent with "senile dementia" or Alzheimer's disease might be considered a normal finding. It might be asked, then, whether or not the patient over 65 with mild sulcal widening on the CT scan might not be called normal. This issue has not been resolved satisfactorily and is somewhat dependent on the interpretation of the reader. Another serious discrepancy between our series and that from London is apparent upon reviewing the num-

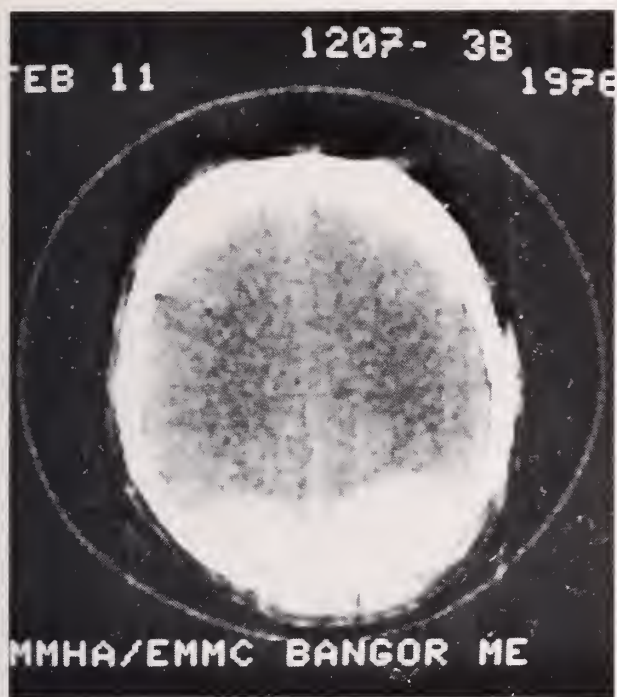


ABSCESS

Contrast enhancement demonstrates a large left parietal lesion with a well vascularized outer capsule and a low density center suggestive of necrosis. At craniotomy, this was a typical well circumscribed brain abscess.

ber of infarctions. Thirteen and one-half percent of the cases here were diagnosed as infarction while only 5.8% of the patients in the London series received this diagnosis. Certainly, the data generated from other studies of stroke would indicate that our data would be more consistent with what might be expected in a cross section of the population.¹¹ The difference in the tumor population, 29.8% at Atkinson Morley's, as opposed to 11.6% at EMMC, is difficult to explain. The British figure would be high if it were to be assumed that this is the percentage of tumors in a population of neurologically ill patients, and may reflect selectivity in early decisions about which patients would be referred for CT studies. The British report also indicates a higher percentage (10.2%) of intracranial hemorrhage, but that is the only other major difference. Their percentage of cases of hydrocephalus is similar to our own.

Other studies report results more similar to our own. New, et al reported the first series of 300 cases at Massachusetts General Hospital in January of 1974.⁷ Although they report an incredible 84.3% abnormal scans, their 14% infarctions, 20% atrophy and 4% hydrocephalus is similar to EMMC percentages. Their series contains a higher number of hematomas, no doubt a reflection of their extremely active neurosurgical service and their wide referral base. Our most recent experience would, however, imply that this present data is a somewhat low estimate of the number of hematomas we shall ultimately be seeing each year. The similarities between the two series would presumably reflect the



EPIDURAL HEMATOMA

Scan through the rostral cerebral hemispheres shows clearly the presence of bilateral dense abnormalities with the typical "inward convex" shape of epidural hematomas. These were discovered post-trauma in a young woodsman with occipital blindness.

varying factors which determine the makeup of the neurological and neurosurgical population in the Northeastern part of this country.

Although emphasis has been made of the safety of this procedure in many of the previous reports, our experience supports this judgment. The procedure itself is painless, and the only difficulty which some patients experience is a claustrophobic discomfort associated with the placement of the head in the scanning apparatus. This complication should not be a problem when the old EMI water reference unit is replaced by the new EMI air reference unit which does not require placement of the head in a constrictive rubber cap.

Although scanning without contrast enhancement is essentially risk-free, there is some risk associated with sedation. Movement can result in considerable scan artefact, and therefore patients who are unable to cooperate require sedation. Ordinarily, an intravenous dosage of diazepam is adequate, but on occasion general anesthesia is necessary. It should be pointed out that in some large pediatric centers, a large number of patients are studied under general anesthesia. As more and more children are done at EMMC, this may become a serious consideration. Our present policy is to schedule general anesthesia only when a "cardiac cocktail" with repeat half dose and supplemental diazepam fail.

Excluding reaction to the sedation, a circumstance we have not yet experienced, the only other

possible complication is an allergic reaction to the intravenous contrast material. The percentage of allergic reactions in our series is quite low, only 0.6% of the total number of patients studied. It is, of course, a requirement to have all of the equipment necessary for a cardiovascular emergency at hand.

In the context of a brief report of this early experience, full comparison of scan results with autopsy findings is impossible. Obviously, not all of the patients were subjected to neurosurgical procedures resulting in histologic diagnosis. For this reason, data on false-positive and false-negative scanning is unavailable. Recent reports, however, emphasize certain limitations of computed tomography in the diagnosis of diseases within the cranium.¹² Problem areas include small lesions, lesions obscured by adjoining structures, abnormalities requiring resolution of vascular detail, cases in which the diagnosis is made but information is incomplete for treatment, cases of incorrect diagnosis, non-neoplastic lesions mistaken for neoplasm, some extracerebral hematomas, occasional false-negative findings and misinterpretation due to technical errors. These authors recommend serial scanning in questionable cases. In our experience to date, small aneurysms, a small subdural hematoma and a small vascular tumor deep in the posterior fossa have been missed. One tumor was obscured by motion on an initial scan but was detected on a repeat study. In summary, pathology can be obscured by motion and proximity of the lesions to structures of high or low density. Abnormalities can be missed by failing to include the pertinent portion of the brain in an examined section. A pathological structure may be overlooked if it is "isodense" with surrounding normal brain. If compared to a standard radiographic system, CT is far superior in that it allows discrimination of structures of similar but slightly different x-ray absorption properties, but it is far inferior in terms of resolution or the number of line pairs that can be resolved in one millimeter. For this reason, small lesions can be lost in the 13 mm. thick sections.

Although admittedly brief, our experience at the EMMC would support the enthusiasm that so many others have voiced regarding the utility of computed tomography. It has and will continue to speed the process of, and accuracy in diagnosing such diverse entities as intracranial neoplastic disease, degenerative disorders, hydrocephalus, cranio-cerebral trauma, intracranial hemorrhage and cerebral infection and infarction. Although our ability to demonstrate the posterior fossa accurately is currently limited, new and more efficient scanning systems will obviate this problem. The explosion of CT technology is just beginning and should provide physicians with greater reliability of diagnosis not only in the brain but throughout the entire body. The future of the technique would seem bright in spite of arguments about cost effectiveness. Con-

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Group B Streptococcal Infection in a Newborn With Few Signs

LEONARDO L. LEONIDAS, M.D.

Group B streptococcal infection in the newborn is a serious disease. It has a mortality of 52%.¹ It is now becoming a common bacterial infection in the neonate in some areas.² One of its usual manifestations is Respiratory Distress Syndrome. This report illustrates a newborn with few signs, but widespread infection.

CASE REPORT

S.G., 7 pounds 12 ounces, Apgar 9/10, born to a 23 year G. Po. after 38 weeks gestation. The mother's pregnancy was normal. There was no premature rupture of membrane.

At 25 hours of age, S.G. was noted by the nurses to have a "poor color" and was "mucousy." The physician on call examined the baby. The physical examination was within normal.

Five hours later, the nurses called the physician again because S.G. is "very jaundice." The temperature was 101 F rectal (incubator 87 F), respiratory rate 84, without retraction, and heart rate 160. Because of the fever, tachypnea, and "worried" facie of the baby, a septic work-up was done (spinal fluid, blood, nose, cord, and ear cultures). Aqueous Penicillin 90,000 units I.M. every 12 hours, and Kanamycin® 20 mg. every 12 hours were started.

PERTINENT LABORATORY RESULTS

1. Initial CBC — 27,000 WBC, 1 Eosinophil, 11 stabs, 72 segmenters, 10 lymphocytes, 2 monocytes.
2. Initial Bilirubin — Total, 15 mg.; direct, 1.5 mg.; indirect 13.5 mg.
3. Cultures: Spinal fluid — presumptive group B beta hemolytic strep. Blood — presumptive group B beta hemolytic strep.

Cord — many staph aureus; many B hemolytic strep not group A, C, or D; moderate number enterobacter cloacae. Nose — many presumptive group B beta hemolytic streptococcus. Ear — many presumptive group B beta hemolytic streptococcus. (Note: The state laboratory in Augusta confirmed the cultures to be group B streptococcus).

4. Initial CSF — 2 WBC, 12 RBC.
5. CSF after treatment — no growth, 0 WBC, 1143 RBC.
6. Nosopharyngeal culture after treatment — no beta streptococcus.
7. Vaginal culture of the mother — moderate number of presumptive group B strep; many beta hemolytic strep not group A, C, or D; many staphylococcus aureus.

The Kanamycin was stopped after the culture reports were known. The temperature remained normal after the antibiotics were started. The respiration became normal on the 6th day. She was never noted to be "toxic." She was discharged on the 15th day asymptomatic with a weight of 7 pounds and 9 ounces.

Group B streptococcal septicemia is a serious disease in the newborn. Early treatment might make this disease not so fatal at all, but cultures should be done before the antibiotics are started.

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COMPUTED TOMOGRAPHY IN MAINE: Initial Clinical Experience — Continued from Page 363

trovercy concerning use of the equipment will undoubtedly continue but the initial experience at EMMC has been both enlightening and gratifying.

ACKNOWLEDGEMENT

The authors would like to thank Ms. Willa Dibner, B.S. and Ms. Cathy Lane, R.T. for their technical assistance.

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Community Medicine in Bangor

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MRS. MIRIAM CAMPBELL† and MR. WILLIAM SHOOK‡

ABSTRACT

As an elective in community medicine, one month was spent doing a history and physical of the City of Bangor. At the end of the month, a problem list and initial plan was formulated. One major outcome of the experience was the feeling on several of the historians' part that a long-term systematic look at the overall health problems of the community could be of service. Included here are the most basic problems with illustrations from a single illness — cervical cancer.

INTRODUCTION

Community medicine was recently described as "concern with the general health of the population at large (and the) needs of people who lack access to the system of medical care."¹ One important aspect of Family Practice is its community orientation. This study was undertaken to provide a foundation for the development of a community medicine aspect to the Eastern Maine Medical Center's Family Practice Residency Program. The focus of the paper is on problems rather than strengths though examples of the latter are numerous.

MATERIALS AND METHODS

The history was taken from several individuals who have responsibility for some aspects of community-level health care. The executive director of a prominent voluntary health agency and the director of the city health department were the primary historians. At the suggestion of the primary historians, more detailed information was obtained from other knowledgeable individuals in the community. Much of the material in the Results part of this paper was obtained from interviews with these persons and is therefore difficult to reference. The other areas of concentration in obtaining the history were other local and state-level government departments and programs having responsibility for health services (e.g., Penquis Community Action Program, Social Security Administration, etc.), the major voluntary health agencies, and individual physicians with particular interest in the health of the community.

The physical was done simultaneously by the col-

lection of existing relatively objective observations on various aspects of the community's health. Wherever possible, well-documented epidemiologic data were obtained from the historians; and, in addition, many possible sources of such data were explored — few proved helpful. Detailed demographic information was available through the 1970 census data. The primary sources of community-wide health statistics came from the admission and discharge data maintained by the community hospitals and from the records of various governmental and voluntary organizations on the particular problems which they address.

RESULTS

Problem 1: Fact-finding and Planning for Community-Wide Health Promotion is Underdeveloped.

The citizens of Bangor spend a large proportion of their resources on health promotion. Where are these resources going? How effective are they? These are at present almost completely unanswerable questions due to the paucity of available data.

At the community level, the determination of priorities is usually based on scanty observations. Judgments on these observations are often made by persons without training in individual or community medicine. Compounding the problem is the absence of a specific organization charged with the responsibility for community-wide health observation or planning. The closest thing to this is the Bangor City Health Department, but this institution has only a small part of its budget allocated for observation and planning efforts.

Outside influences are powerfully shaping local priorities and mechanisms largely through federal-level programs. State and regional-level programs are also influential (e.g., Crisis Illness Program, Penquis C.A.P.). Since these programs often reflect federal-level thinking, the health care plans of the local area are being most strongly affected by this outside force.

A disease of relatively well understood natural history, method of diagnosis, and treatment, will be used as an illustration — cervical cancer. To deal with cervical cancer as a community problem, several observations and plans are necessary. The incidence of the problem helps put it in perspective. Though this information could be obtained easily from the Cancer Registry maintained by a local hospital, it was unknown at the time of the study. (Eight new cases with Bangor addresses diagnosed, treated, and reported to registry per year — 20 yr. average.)²

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The stage at which diagnosis is being made helps inform the community of its success in detection. This also is available from the Cancer Registry. (20-yr. average for patients with Bangor addresses — in situ, 57%; localized, 18%; regional, 22%; metastatic, 3% — most recent 5-yr. average is not significantly dif.)³

The number of providers of services, their method and cost of screening, and their population served must be known to avoid gaps and duplication. This information has not been gathered together in any known study. The public must be well informed on their alternatives in obtaining access to screening and diagnostic services. Based on interviews, there are many misconceptions on the types of services available even among the people directly responsible for community-level health care. The characteristics of the late stage cases might be used to alter community screening methods, but no study of these cases has been done as far as is known.⁴ In contrast to the absence of community-wide activity in many areas is the American Cancer Society's promotion of public knowledge of cervical cancer screening methods.

In summary, many of the observations necessary to plan a community approach to cervical cancer have not been made. No known plans exist to remedy this situation or to use the existing observations to try to improve the success of the community in dealing with the problem.

Without accurate and timely observations, meaningful planning cannot occur. Without a clear division of planning responsibility, successful local health care is unlikely at any cost. Plans are discussed below.

Problem 1A: Coordination of Health Care Providers Underdeveloped.

There are many examples of coordinated health care delivery in Bangor, but this is not the rule. Instances in which several individual providers and institutions may be attempting to deal with the same problem without knowledge of each other's efforts is an example. Another coordination problem is the interaction of social welfare programs with health care programs. While great strides have been made through the social service department of the Eastern Maine Medical Center, coordination of these two types of service in the ambulatory programs is often weak.

Returning to cervical cancer, the lack of coordination, is well illustrated. In Bangor, the cervical cancer detection, treatment, and followup team is complex. If a patient makes and maintains contact with any one of the detection providers, a highly coordinated approach prevails. In cervical cancer, the coordination problem is at the level of detection and, to a lesser degree, in the followup area. The Family Planning Center, run by the regional community action program (Penquis C.A.P.), has a very systematic program to reach a certain part of the cervical cancer-risk population: women with a need

for birth control and, implicitly, the lower socioeconomic groups. Outside this, access to a regular detection program is unsystematic. Unless a patient is motivated and resourceful, she may not be able to find access to a screening program. Evidence of this is the fact that only 26 percent of 567 women seen in an American Cancer Society Pap Test Clinic in 1971 had had a Pap in the previous one year. Forty-one percent had not had one in the past three years. Of these, twenty-four percent had never had a Pap.⁵ The fact that 25 percent of the cancers known to the registry in the past 20 years were beyond the localized stage at diagnosis is also suggestive.

Once a case is found, followup is very systematic. However, it does not extend to using the case as a way of understanding how to improve the detection system. That this is the case is suggested by the fact that no study of the discovered, advanced stage cases is available.

A part of the larger problem of underdeveloped community diagnosis and planning is the lack of coordination of the existing delivery system. This problem leads to less than optimal care despite the expenditure of relatively large amounts of community resources. Plans are discussed below.

Problem 1B: Maldistribution of Services.

Maldistribution occurs in many forms — age, sex, economic, etc. The etiology of the maldistribution problems is, like the problems above, complex and rooted as much in history as in the present. Again, the lack of community-wide perspective and the confusion generated by federal and state-level programs are important. This set of problems is best discussed by example.

Cervical cancer is a disease with fairly well-known epidemiologic characteristics. It is a disease which is more common among the lower socioeconomic status groups⁴ and among relatively young women (peak age 51). A community wishing to achieve the highest number of cases found and treated at the lowest cost would focus on a risk group defined by age and socioeconomic status — perhaps age 50 plus or minus 15 and the lower half of the income structure. Yet, in Bangor, little is done to assure that this group has relatively easy access to diagnostic facilities. Other than the family planning program mentioned above, all detection providers are more difficult to work with as socioeconomic status decreases. Numerous types of barriers make this the case.⁶ The finding in the American Cancer Society Pap Test Clinic that many women in the high-risk groups were unlikely to have had a recent Pap is evidence of this weakness. Of the women in the 31-50 year age group, 30 percent had not had a Pap in the past three years; and, of this group, 17 percent had never had a Pap. It is interesting to note that the percentage of advanced stage cervical cancers diagnosed in Bangor residents has remained about 25 percent of the total

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cases since 1960.⁷ During this interval, the number of Pap Smears done by the major pathology labs in the City of Bangor has risen from 2,300 in 1960 to over 30,000 in 1975. The percentage of these cytologies done on Bangor residents is at present unknown.

Maldistribution of services exists in many forms in the community. Significant maldistribution problems should be located, described, and initial plans formulated. The available data on cervical cancer screening suggests maldistribution of service to the high-risk population. This is one area which deserves further evaluation and planning. Plans are discussed below.

PLANS

Effective community-wide study and planning probably depends on having a group of professionals with responsibility for the task. Short of this, attention is often unsystematic and results of studies are frequently difficult to retrieve or are easily lost. Community-wide interest is part of Family Practice and therefore development of a strong community medicine program in the EMMC's Family Practice Residency Program is part of the answer. Conferences, lectures, elective block rotations, and possibly required block rotations are mechanisms under consideration. Communication between diverse elements of health and medical care systems, increasing the existing data on community problems, and increasing the knowledge and sensitivity of Family Practitioners to these problems are the overall goals. But this program must ultimately be orientated to a relatively narrow aspect of health services. A new approach with broader perspectives serving the whole community seems necessary. This might be a strong community medicine department organized either as a separate institution or possibly as part of EMMC, the Bangor City Health Department, the Bangor-Brewer TB and Health Association, or Penquis C.A.P. The function of this organization would be to collect and analyze data on community-wide health problems, advise on dealing with these problems, and help

coordinate the delivery of services. While health planning is a prime interest of the federal government, local-level study and implementation of programs seems a weak area of this effort. This sort of institution could buffer the divisive forces and augment the positive forces of state and federal health programs in many ways. Several alternatives exist in defining the community to be served, and the proposal here is the basis for discussion only. Many aspects of Bangor community life involve a group of approximately 100,000 persons living in a 30-mile radius of the city. This group constitutes the labor market, retail trade area, and primary service area of the two major general hospitals in the city.⁸ It would seem logical, though complex, to have this be the community served.

COMMENT

As our communities and health and medical services have become more complex, various levels of health specialties have developed — notably state, federal, city, and county health departments. To serve modern population groupings, new levels seem necessary. The greater Bangor-Brewer metropolitan area may constitute a community which could benefit from overall study, planning, coordination, and implementation of health promotion programs.

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Reminder to M.M.A. Members

CONTINUING MEDICAL EDUCATION ACTIVITY REPORT

The bylaws of the Maine Medical Association were amended in June of 1973 as follows: Chapter I, Section 11, — "Each member of the Maine Medical Association shall be required to report his activities in continuing medical education every year according to a format provided by the Committee on Continuing Medical Education."

Only active, dues-paying members are required to report this year.

Please fill in your activity report promptly and return to the M.M.A. office, P.O. Box 250, Brunswick, Maine 04011.

Antimicrobial Spectrum, Pharmacology, and Therapeutic Use of Antibiotics

I. Tetracyclines

MICHAEL BARZA, M.D.* and RICHARD T. SCHEIFE, Pharm.D.**

In 1948, Benjamin Duggar, working at Lederle Laboratories, isolated chlortetracycline from the actinomycete *Streptomyces aureofaciens*. Since his discovery, much effort has been expended to modify the chlortetracycline molecule in order to alter its pharmacological and therapeutic properties.

MODE OF ACTION

The antimicrobial effect of the tetracyclines is due to their inhibition of ribosomal protein synthesis (i.e., they block "recognition").^{1,2} In contrast to most other antibiotics, the tetracyclines are also capable of interfering with mammalian as well as bacterial protein synthesis,^{2,3} which may explain their potential ability to impair wound healing and to produce a catabolic state in patients with renal failure.

On the basis of their behavior *in vitro*, the tetracyclines are considered "bacteriostatic" rather than "bactericidal" antibiotics.⁴ This characteristic is in accordance with their poor therapeutic effect in bacterial endocarditis, serious staphylococcal infections, and in eradicating the streptococcal carrier state.⁵

The tetracyclines are more active *in vitro* in an acid, rather than an alkaline, medium;⁶ this may be relevant to the treatment of urinary tract infections.⁷

BACTERIAL RESISTANCE

There are three principal means by which bacteria may be resistant to antimicrobial agents:² (1) alteration of the target (ribosome) so that it is no longer susceptible to the action of the drug; (2) production of an enzyme (or enzymes) which degrades the antibiotic; (3) a change in the permeability of the bacterium to the agent. Acquired resistance to the

tetracyclines appears to occur largely through the second and third of these mechanisms.^{2,8} The genetic information for such resistance is often carried in an extra-chromosomal DNA fragment called a "plasmid." One class of plasmids found in gram-negative bacilli, the R factors, are of particular importance because: (a) they are capable of expressing resistance to many unrelated antibiotics and (b) they can be transmitted "horizontally" throughout colonies of the same, or related, gram-negative bacilli with great rapidity. The potential epidemiological problems associated with "infectious drug resistance" mediated by R factors are evident.⁹ A somewhat different kind of transmission of the genetic information for antibiotic resistance is found in staphylococci, in which the plasmid can be carried piggyback upon a bacterial virus (bacteriophage).

There is abundant evidence that the prevalence of resistant strains fluctuates with the extent of use of tetracyclines in the community and in hospitals. Whether the inclusion of these agents in animal feed has affected this pattern is a subject of debate.¹⁰

IN VITRO ACTIVITY

The tetracyclines are "broad-spectrum" antibiotics with activity against bacteria, rickettsiae, chlamydia, actinomycetes and even protozoa. The susceptibility patterns of a number of common bacterial isolates is summarized in Table 1. It should be noted that the designation of "resistant" is based on the somewhat arbitrary concept of "easily achievable serum levels;" thus, infections at certain sites (e.g., urinary tract) may be cured despite apparent "resistance" *in vitro*. Also, the frequency of resistant strains among common pathogens may vary somewhat from hospital to hospital, and community to community. Because of widespread resistance, the tetracyclines cannot be relied upon as initial therapy for infections due to most gram-positive cocci, gram-negative facultative† bacilli, or anaerobes. Indeed, fully a third of anaerobic strains found in the mouth are resistant to these agents.²¹ The majority of gonococci and strains of *H. influenzae*

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†A facultative bacterium is an organism which can grow aerobically or anaerobically.

TABLE 1

IN VITRO ACTIVITY OF TETRACYCLINES ^a	
Organisms	In Vitro Activity
<i>Gram-positive cocci</i>	
Staphylococcus aureus ^{4,6,11,12} (penicillin sensitive and penicillin resistant)	90% inhibited by minocycline; only 50% susceptible to other congeners
Beta-hemolytic streptococci Group A ^{13,14}	80% highly susceptible to all congeners; 10-20% resistant (up to 30% in some studies)
Beta-hemolytic streptococci Group B, C, G	Variable, many organisms resistant (especially Group B)
Pneumococcus ^{15,16}	Small percentage (about 5%) resistant (0-20% in various reports)
Enterococcus	Virtually all resistant
<i>Gram-negative cocci</i>	
Meningococcus ¹⁷	Up to 50% resistant
Gonococcus ^{4,18,19}	Most strains sensitive, but increasing prevalence of relative resistance
<i>Gram-positive bacilli</i>	
Clostridium perfringens ^{15,20,21}	Increasing resistance, as many as 10-20% in some areas (40% in one study ³)
<i>Gram-negative bacilli</i> ⁴	
Escherichia coli	Variable
Klebsiella pneumoniae	Variable
Enterobacter aerogenes	Variable, most resistant
Proteus mirabilis	Variable
Pseudomonas aeruginosa	Most resistant
Hemophilus influenzae	Most strains sensitive; oxytetracycline and tetracycline may be somewhat less inhibitory than other congeners
Bacteroides fragilis ²¹ ("gut")	Approximately half of strains resistant
Bacteroides melaninogenicus ²¹ ("mouth")	10-40% of strains resistant; minocycline slightly more active than other congeners

^aTetracyclines considered in preparation of this table are minocycline, doxycycline, chlortetracycline, demeclocycline, methacycline, tetracycline, and oxytetracycline. Susceptibility is for concentrations attainable in serum.

TABLE 2

HUMAN PHARMACOLOGY OF SIX TETRACYCLINES						
Characteristic (references)	Minocycline	Doxycycline	Chlortetracycline	Demeclocycline	Tetracycline	Oxytetracycline
Trade names	Minocin [®] Vectrin [®]	Vibramycin [®]	Aureomycin [®]	Declomycin [®]	—	Terramycin [®]
Usual oral dosage	200 mg initially, then 100 mg every 12 hours	100 mg every 12 hours first day, then 100 mg/day as a single dose or 50-100 mg every 12 hours	250-500 mg four times a day	150-300 mg four times a day	250-500 mg four times a day	250-500 mg four times a day
Usual IV dosage ^a	200 mg initially, then 100 mg every 12 hours	200 mg first day, then 100-200 mg/day	250-500 mg every 12 hours	—	250-500 mg every 12 hours	250-500 mg every 12 hours
Percentage of oral dose absorbed (empty stomach) (25-27)	100	93	30	66	77	58
Half-life in serum, hours with normal renal function (26,28,29)	19	15	7	15	10	9
Percentage of parenteral dose excreted in urine (25,26,29,30)	5-10	35	18	42	60	70
Non-renal routes of elimination (26,27,31)	Probably metabolized	Secreted into intestinal lumen	Excreted into bile	—	—	—
Peak level of drug in spinal fluid as a percentage of that in serum (26,32-34)	25	12-20	5	?	10	10

^aTetracyclines are usually not administered intramuscularly because they are highly irritating and irregularly absorbed by this route. Intravenous dosage of chlortetracycline, tetracycline and oxytetracycline may be doubled for serious infections. Chlortetracycline is unstable in neutral or alkaline solutions.

TABLE 3

ADVERSE EFFECTS OF TETRACYCLINES^a

Tetracycline	ADVERSE EFFECTS						
	<i>Interacts with food (exclusive of polyvalent cations)</i>	<i>Disturbances of bowel flora</i>	<i>Photo- toxicity</i>	<i>Accumulates in renal failure</i>	<i>Anti-anabolic effect</i>	<i>Pediatric Tooth Discoloration</i>	<i>Vestibular toxicity</i>
Tetracycline	++	++	++	+++	+++	+++	0
Chlortetracycline	++	+++	++	0	+++	++	0
Oxytetracycline	+	+++	++	+++	+++	+	0
Demeclocycline	+++	++	++++	+++	+++	+++	0
Doxycycline	0+	+	+++	0	0	+	0
Minocycline	0+	+	+	0	+++	++	++++
Methacycline	++	++	++	+++	+++	++	0

^aPropensity of various tetracyclines to cause selected adverse effects.

are still susceptible to the tetracyclines.

Efforts to change the antibacterial spectrum of the tetracyclines have been frugally rewarded. Minocycline, however, appears to be significantly more active than other congeners against *Staph. aureus*.^{4,11,12} It is also somewhat more inhibitory to anaerobic organisms^{21,22} and to *Nocardia*^{23,24} than are other tetracyclines. Minocycline and doxycycline are the most active members of their class against facultative gram-negative bacilli.^{4,6,11,12} There are insufficient controlled clinical comparisons to determine whether these *in vitro* differences are relevant to the treatment of infections in humans.

PHARMACOLOGY

Absorption

With the exception of chlortetracycline, the tetracyclines are well absorbed by mouth (Table 2). Food, and various polyvalent cations, such as are found in antacids, iron tablets and milk, impair the uptake of this class of antibiotics.³⁵⁻⁴⁰ Although food interferes less with the absorption of minocycline and doxycycline than with that of the other analogs, the interaction with cations may be substantial for all of the tetracyclines.³⁶ The administration of iron by mouth lowers serum levels of doxycycline even when the latter is given intravenously; when iron tablets are taken three hours before or after ingestion of a tetracycline antibiotic, an interaction is still demonstrable with doxycycline, though not with tetracycline hydrochloride.³⁶ This discrepancy may be due to the prominent role of the intestine in the elimination of doxycycline, but not of tetracycline (see below).

Elimination

From 20-50% of an oral dose of any of the tetracyclines is eliminated in the feces; this represents a combination of unabsorbed drug and antibiotic excreted via the biliary tract or intestine.^{25,35}

The tetracyclines differ substantially in their modes of elimination; this has consequences for the half-life of the drug in various degrees of renal dysfunction and dictates the normal dosing interval. The oldest tetracycline (chlortetracycline) and the

two newest compounds (minocycline and doxycycline) are eliminated largely by non-renal routes while the other agents are mainly excreted in the urine (Table 2). Thus, demeclocycline, tetracycline and oxytetracycline produce greater urinary antibacterial activity than the other congeners. Doxycycline exhibits an unusual mode of elimination: it is excreted into the intestine where it is chelated by and eliminated with the feces.

Tetracyclines are actively secreted into the bile and are available for enterohepatic recirculation;³⁷ this phenomenon accounts, in part, for their prolonged duration of action.³⁸

Distribution

The extent to which any substance penetrates body cells, tissues, and in particular, privileged sites such as the brain, eye, and prostate, is highly dependent on the lipid-solubility of the compound. Minocycline and doxycycline are the most, and oxytetracycline is the least lipid-soluble of the tetracyclines.⁴¹ Penetration of the spinal fluid⁴² (Table 2), brain,⁴² eye⁴² and prostate^{43,44} are most readily accomplished by the more lipid-soluble tetracyclines. Serum protein binding plays a lesser role in the distribution of tetracyclines than it does with the penicillins, because differences among the congeners are not great (55-82% binding for all but oxytetracycline which is 30% bound)^{25,26} and because these agents appear to bind to various other intra- and extra-cellular constituents.^{42,43,45}

The tetracyclines readily enter fetal tissues and breast milk⁴³ (see adverse effects). Minocycline displays exceptionally good penetration of saliva,⁴⁶ which makes it an attractive agent for the treatment of meningococcal carriers; unfortunately, the drug also frequently causes vertigo,⁴⁷ presumably because of its ready traversal of the blood-brain barrier. The tetracyclines are deposited in maturing bone structures.⁴⁰ The clinical significance of this observation is unknown.

DOSAGE

Patients with Normal Renal Function

Adherence to the schedules in Table 2 will generally produce peak serum levels of 3-4 $\mu\text{g/ml}$ in

adults with normal renal function.^{25,26,28} The differences in the frequency of dosing (e.g., twice a day for minocycline versus four times a day for tetracycline) and in the total daily dosage of the tetracyclines are largely (but not solely) the result of differences in their half-lives.²⁷

Patients with Renal Insufficiency

Tetracycline antibiotics should generally be avoided in patients with renal insufficiency; most of them accumulate in these individuals and may exacerbate the renal dysfunction directly, and may cause a catabolic state with acidosis, increasing azotemia, and death.^{48,50} The administration of more than 1 g of tetracycline per day intravenously to pregnant women with renal infections has also caused this catastrophic picture.⁴⁸ Although chlor-tetracycline is largely eliminated through the biliary tract,²⁷ it, too, is capable of producing these effects.⁵¹ For the rare individual with renal dysfunction who requires a tetracycline, doxycycline may be administered in usual doses without fear of drug accumulation, enhanced renal dysfunction or catabolic acidosis.^{31,48} The same is probably true of minocycline though some controversy persists.^{48,52,53}

There are only fragmentary data concerning the dialyzability of the tetracyclines. These suggest that none of the congeners is readily removed by hemo- or peritoneal dialysis except for oxytetracycline which is moderately hemodialyzable.^{48,54}

ADVERSE REACTIONS

Adverse reactions to tetracyclines are common, and in certain generally predictable settings, may be serious. The relative propensity of various analogs to produce certain of these effects is shown in Table 3.

Gastrointestinal Effects

Nausea, vomiting, anorexia, and an "unpleasant taste" are the most common side effects of the tetracyclines.^{37,55} Recently, esophageal ulceration has been attributed to the tetracyclines;⁵⁶ nocturnal ingestion of antibiotic capsules and pre-existing pathology (generally hiatus hernia) were thought to be contributing factors.

Candidiasis and Enterocolitis

Oral candidiasis (thrush) and vulvovaginitis are not infrequent, presumably due to alterations in the normal microbial flora induced by the tetracyclines.⁵⁷ A similar mechanism may be responsible for the catastrophic entity of enterocolitis following administration of tetracyclines;^{37,58,59} for reasons that are not clear, this side effect appears to have occurred much less frequently during the past decade. Although doxycycline^{35,58,61} and minocycline seem to produce fewer alterations of the fecal flora than do other analogs, it has not been shown that they produce fewer of the related side effects.

Phototoxicity

This is an occasional consequence of tetracycline therapy and probably results from accumulation of these agents in the skin.^{13,49,60,62,63} A sunscreen preparation containing para-aminobenzoic acid or ordinary windowglass affords good protection in susceptible patients.⁶⁴

Accumulation

The tendency of the tetracyclines to accumulate in patients with renal insufficiency has been discussed above.

Hepatotoxicity

The toxic effect of tetracyclines on the liver is characterized by fatty infiltration without necrosis. Hepatotoxicity has been observed following large doses (> 2 g per day) intravenously, or "normal" doses in patients with renal impairment, especially in pregnant or malnourished individuals.⁶⁵⁻⁶⁹

Tooth Mottling

Tetracyclines are capable of binding to the calcium in teeth and bones, and of causing damage to these structures, especially during growth. These antibiotics should be avoided in children less than 7 years old since mottling of the permanent teeth may occur; after this age, the cosmetically important anterior teeth have been formed.^{49,70,71} Doxycycline and oxytetracycline may carry less risk in this regard than other analogs.⁷²

*Tetracyclines should not be given to pregnant women, unless no suitable substitute is available, because these patients are particularly liable to develop catabolic acidosis and liver damage. Furthermore, there is a high risk of producing discoloration of the deciduous teeth in the offspring, especially after the fourth month of gestation.*⁷³

Pseudotumor Cerebri

This has been observed occasionally in infants given tetracyclines. Signs and symptoms usually remit within a few days of cessation of therapy, although the papilledema may be more persistent.^{13,49,74,75}

Vestibular Toxicity

Minocycline exhibits a unique potential to cause vestibular toxicity in up to 90% of recipients in some series.⁷⁶⁻⁷⁹ Nausea, vomiting and vertigo appear to be dose-dependent and reversible within 48 hours of discontinuing the drug.⁷⁹

Other Adverse Reactions

The administration of outdated tetracycline has caused a Fanconi-like syndrome, presumably due to the presence of degradation products of the antibiotic.^{37,80,81} Acute, reversible nephrogenic diabetes insipidus has resulted from the use of one congener, demeclocycline.^{49,82,83} Indeed, this compound has been used in the treatment of the syndrome of in-

TABLE 4

INDICATIONS FOR THE USE OF TETRACYCLINES^a

<i>Tetracyclines – drugs of first choice</i>	<i>Tetracyclines – a good alternative (best choice)</i>	<i>Tetracyclines – not preferred drugs</i>
Bacterial infections:	Chancroid (sulfonamides)	Pharyngitis
Plague — with streptomycin	Glanders (sulfonamides)	Pneumonia
Melioidosis — with other antibiotics	Tularemia (streptomycin)	Staphylococcal infection
Brucellosis — with or without streptomycin (trimethoprim-sulfamethoxazole alone is a satisfactory alternative) ⁷²	Pertussis	Endocarditis
Granuloma inguinale (southeastern USA)	<i>HEMOPHILUS INFLUENZAE</i> RESPIRATORY TRACT INFECTIONS (ampicillin)	Meningitis
Cholera (<i>Vibrio cholerae</i>)	SYPHILIS (penicillin G)	Anaerobic infections
Bartonellosis	GONORRHEA (penicillin G)	
Borreliosis, relapsing fever	MENINGOCOCCAL PROPHYLAXIS — minocycline (sulfonamide; rifampin)	
occasionally encountered in USA	Leptospirosis (penicillin G)	
Non-bacterial infections:	Anthrax (penicillin G)	
<i>MYCOPLASMA PNEUMONIAE</i>	Listeriosis (penicillin G or ampicillin)	
PNEUMONIA	Actinomycosis (penicillin G)	
GENITAL MYCOPLASMAS	Nocardia (sulfonamides or various combinations) ^{23,24}	
RICKETTSIAL INFECTIONS	Intestinal amebiasis (metronidazole — tetracycline with diodoquin) ⁸⁹	
Chlamydial infections (trachoma, inclusion conjunctivitis, lymphogranuloma venereum, psittacosis)		
Syndromes:		
ACNE VULGARIS		
MALABSORPTION SYNDROMES (Whipple's disease, blind loop syndromes, tropical sprue)		
UNCOMPLICATED URINARY TRACT INFECTION		
ACUTE EXACERBATIONS OF CHRONIC BRONCHITIS		

^aIf alternative therapy is available, tetracyclines should not be used in pregnant women, or in children below the age of 7 years. Doxycycline should be used in individuals with renal impairment. Indications in all capital letters are the most commonly encountered infections.

appropriate ADH secretion.^{84,85}

INTERACTIONS

Tetracyclines may cause a false-positive urine glucose test with cupric sulfate reagents (Clinitest®) and a false-negative test with glucose oxidase reagents (Tes-Tape®).⁸⁶ Interference of the tetracyclines with certain clotting factors have been reported.⁸⁷ Recently, it has been demonstrated that the half-life of doxycycline is significantly shortened by co-administration of phenobarbital, phenytoin, or carbamazepine.^{88,89} Interaction of tetracyclines with iron, food, milk, and antacids has been noted previously.

INDICATIONS

The tetracyclines should be avoided, if possible, in pregnant women and in children less than 8 years of age, as well as in individuals with liver disease. Where the use of "tetracycline" is recommended in the following discussion, this refers to tetracycline hydrochloride; a comparable dose of any of the congeners is equally effective. Specific regimens are generally available in standard textbooks of medicine.

The tetracyclines represent a therapeutic "first choice" in relatively few situations. Most of the bacterial infections listed in the first column of Table 4 will be encountered rarely, if ever, by physicians practicing in North America. In contrast, these drugs constitute a first choice in the therapy of many common non-bacterial infections. *Mycoplasma*

pneumoniae pneumonia ("primary atypical pneumonia") responds to tetracyclines as well as to erythromycin.⁹¹ The genital mycoplasmas, including *M. hominis* and the so-called "T strains," have been implicated in acute salpingitis, infertility, low birth weight babies, habitual abortion, and other pelvic inflammatory disease in the female.^{92,93} Their role in these syndromes and the value of tetracycline therapy remain controversial.

Non-gonococcal urethritis ("nonspecific urethritis") overlaps with the entity of post-gonococcal urethritis.⁹⁴ The major candidates as etiologic agents are the chlamydiae and genital mycoplasmas. A tetracycline provides effective therapy in about 80% of cases.^{94,95} The oral dosage of tetracycline hydrochloride is 1.5 g initially, followed by 0.5 g four times a day for 7-10 days. Erythromycin appears to be a useful alternative.⁹⁵

Rickettsial infections (Rocky Mountain Spotted Fever, rickettsialpox, typhus and Q fever in the USA) respond well to tetracyclines or chloramphenicol if treated early. Tetracyclines are also drugs of choice for chlamydial infections (psittacosis, lymphogranuloma venereum, trachoma and inclusion conjunctivitis); in the latter two diseases, tetracycline is best applied topically. Some authors consider sulfonamides to be the optimal therapy for trachoma.

The tetracyclines offer a useful therapeutic alternative for a number of diseases (Table 4; drugs in parentheses are the usual first choice). *Hemophilus influenzae* infections of the upper or lower respira-

tory tract in children should be treated with a drug other than a tetracycline (e.g., ampicillin). In adults, the organism is usually encountered in acute exacerbations of chronic bronchitis; a tetracycline is generally effective for these patients. Penicillin-allergic patients may be treated for early or latent syphilis with tetracycline, 2 g daily for 15 days; erythromycin is an excellent alternative.

Uncomplicated anogenital gonorrhea in the penicillin-allergic patient generally responds to single-dose therapy with spectinomycin, or to the following regimen of tetracycline hydrochloride: 1.5 g by mouth initially, then 0.5 g four times a day for four days.⁹⁶ Gonococcal pharyngitis requires more prolonged therapy.⁹⁶ A tetracycline or erythromycin are also satisfactory alternatives for the treatment of acute salpingitis and disseminated gonococcal infection.⁹⁶ Pregnant patients allergic to penicillins should not be given a tetracycline; erythromycin, cefazolin or spectinomycin can be used for the treatment of gonorrhea in these individuals.⁹⁷

Meningococcal prophylaxis presents one of those instances in which a particular congener, namely minocycline, appears more effective than other tetracyclines; however, the apparent frequency of vestibular side effects with this drug has led to the recommendation that rifampin be used for strains not known to be sensitive to sulfonamide.⁴⁷ The dosage of rifampin is 600 mg twice a day for two days in adults, and 10 mg/kg twice a day for two days in children.

The tetracyclines have been strikingly effective in various malabsorption syndromes including Whipple's disease,⁹⁸⁻¹⁰⁰ blind loop syndromes due to bacterial overgrowth,¹⁰¹⁻¹⁰³ and tropical sprue.¹⁰⁴ There is accumulating evidence of the value of low-dose tetracycline therapy in the treatment of acne vulgaris; data from controlled studies have been summarized elsewhere.¹⁰⁵

Tetracyclines are as effective as sulfonamides, ampicillin, or even penicillin G,¹⁰⁶ in the treatment of uncomplicated urinary tract infections; indeed, approximately 85% of such infections respond to treatment with virtually any antimicrobial agent.¹⁰⁷ A favorable response is sometimes encountered despite apparent resistance of the organism *in vitro*; this probably reflects the attainment of high antibacterial levels in the urine. Although supportive data are lacking, we favor a bactericidal antibiotic such as ampicillin, a cephalosporin, or gentamicin, for patients with apparent pyelonephritis. It must be recognized that a large proportion of patients treated for urinary tract infection will develop a reinfection or (less commonly) a relapse;¹⁰⁷ generally speaking, the recurrence is due to a bacterium which is still sensitive to the first drug.¹⁰⁶ An approach to therapy of patients with repeated recurrences has been described recently.¹⁰⁸

It is possible to find both support and refutation for almost every regimen conceivable in the prophylaxis or treatment of exacerbations of chronic bron-

chitis. Among the few things agreed upon is the necessity of treatment of acute exacerbations with some antimicrobial agent. There is little therapeutic difference among tetracycline, ampicillin, chloramphenicol or penicillin G with streptomycin for acute episodes.¹⁰⁹⁻¹¹² Amoxicillin, trimethoprim-sulfamethoxazole, or a cephalosporin probably afford adequate therapy, also.¹¹¹ For patients with frequent exacerbations during the winter, chronic seasonal administration of a broad-spectrum antibiotic has been found helpful¹¹³⁻¹¹⁷ by some groups, but others have found such therapy of little value.¹¹⁸ A common approach is to advise that a defined course of antibiotic be taken at the onset of any "cold." In one study, ampicillin or tetracycline were found not to be superior to placebo when taken in this way;¹¹⁰ in another, this form of therapy was less effective than continuous prophylaxis.¹¹⁵ There appears to be no demonstrable effect of long-term antibiotic administration on the ultimate progression of chronic bronchitis.^{118,119} In summary, acute exacerbations of chronic bronchitis should be treated with a broad-spectrum antibiotic; the value of prophylaxis on either the frequency or severity of acute exacerbations or the progression of lung disease remains to be proven.

The use of the tetracyclines for prophylaxis of secondary bacterial infections in children with cystic fibrosis (mucoviscidosis is discussed elsewhere).^{120,121}

Misuse of the tetracyclines is frequent. There is no place for prophylactic administration of these drugs to individuals with viral infections; the rate of development of bacterial superinfection is not reduced, and infection with resistant organisms may be encouraged.^{122,123} Tetracyclines are a poor choice of therapy for pharyngitis or pneumonia, because beta-hemolytic streptococci and pneumococci are sometimes resistant to these agents. Similarly, the prevalence of tetracycline-resistant strains militates against their value in anaerobic infections. The tetracyclines are never a drug of choice for staphylococcal infections. Indeed, because of their toxicity, they should rarely be used aside from the circumstances noted above (see Table 3).

SELECTION OF A TETRACYCLINE

In terms of the antibacterial efficacy of the various congeners, minocycline offers some advantage in the therapy of staphylococcal¹²⁴ and *Nocardia* infections. However, staphylococcal infections are *not* an indication for the use of any tetracycline and clinical experience is insufficient to document their use in *Nocardia* infections.¹²⁵ With regard to their pharmacology, it might seem wise to avoid minocycline and chlortetracycline for urinary tract infections because of their minimal excretion by this route; clinical data, however, do not support this caveat. For the treatment of an infection of the central nervous system, eye, or prostate, minocycline or doxycycline would appear to offer benefit over

TABLE 5

RELATIVE COST TO THE PHARMACIST OF ONE WEEK'S
THERAPY WITH THE VARIOUS TETRACYCLINES

Tetracycline	Dose ^a	Cost
Tetracycline	250 mg four times a day	\$1.15
Chlortetracycline	250 mg four times a day	\$4.31
Oxytetracycline	250 mg four times a day	\$2.74
Demeclocycline	150 mg four times a day	\$5.00
Doxycycline	100 mg Stat, then 100 mg twice a day	\$4.90
Minocycline	100 mg Stat, then 100 mg twice a day	\$2.52
Methacycline	150 mg twice a day	\$2.30

^aThe lower end of the dosage range is given; higher doses are frequently indicated (see Table 2).

the other compounds because of differences in penetration. The analogs differ somewhat in the kind and degree of their toxicities. This can be used to advantage in mitigating specific adverse effects in some patients. Although doxycycline appears to incur somewhat fewer side effects than many of the other agents, clinical data are not adequate to warrant advocacy of this drug over other analogs.

Overall, there is one clinically pertinent difference among the tetracyclines, namely, the fact that doxycycline, and probably minocycline, can be given in full dosage and with minimal risk to the patient with renal impairment. Although some physicians have felt that patient compliance was facilitated by the use of doxycycline or minocycline since they are given only twice (or in selected circumstances, once daily) daily, we have generally used the least expensive analog (Table 5), tetracycline hydrochloride, in patients with normal renal function.

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II. Penicillins

MICHAEL BARZA, M.D.

INTRODUCTION: THE FOUR GROUPS OF PENICILLINS

Few discoveries have had a greater impact upon the practice of medicine than that of the penicillins. The first to be derived, the so-called "natural penicillins," afforded definitive therapy for a number of previously lethal infections (Figure 1). With the increasing prevalence of penicillin-resistant strains of *Staphylococcus aureus* during the 1950's, efforts were undertaken to produce congeners which would not be susceptible to the penicillinase elaborated by these organisms. The original "penicillinase-resistant penicillin" was methicillin (1960); it was followed by nafcillin and the isoxazolyl penicillins (oxacillin, cloxacillin, dicloxacillin, flucloxacillin). The latter group contains closely related substances which differ only in the number of halogen substitutions (chlorine, fluorine).

The past decade has witnessed a new era in the evolution of the penicillins with the introduction of the "broad-spectrum" groups. The first comprises ampicillin and amoxicillin, as well as certain other agents which are broken down to ampicillin (e.g., hetacillin, pivampicillin); these drugs are active against *Haemophilus influenzae* and *Escherichia coli*. The most recent additions to the class, carbenicillin and ticarcillin, exhibit a spectrum which includes many Gram-negative bacilli, including *Pseudomonas*.

MECHANISM OF ACTION

The penicillins are bactericidal antibiotics, that is, ones which do not simply interrupt the proliferation of bacteria but actually destroy them. They do so by interfering with the activity of enzymes (e.g., transpeptidase) which cross-link the peptidoglycan molecule of the cell-wall into a stable monomer.¹ Their activity, therefore, requires that the bacteria be growing. Gram-negative organisms, being endowed with a fairly strong lipopolysaccharide coat, are less dependent than Gram-positive organisms upon the integrity of the peptidoglycan molecule for resistance to osmotic lysis; correspondingly, they are less susceptible to the action of penicillins than Gram-positive bacteria.² Sensitive strains show different degrees of inhibition by the various analogs of penicillin; the reasons for this are not clear, though a correlation can be shown with the lipid solubility of the particular antibiotic.³

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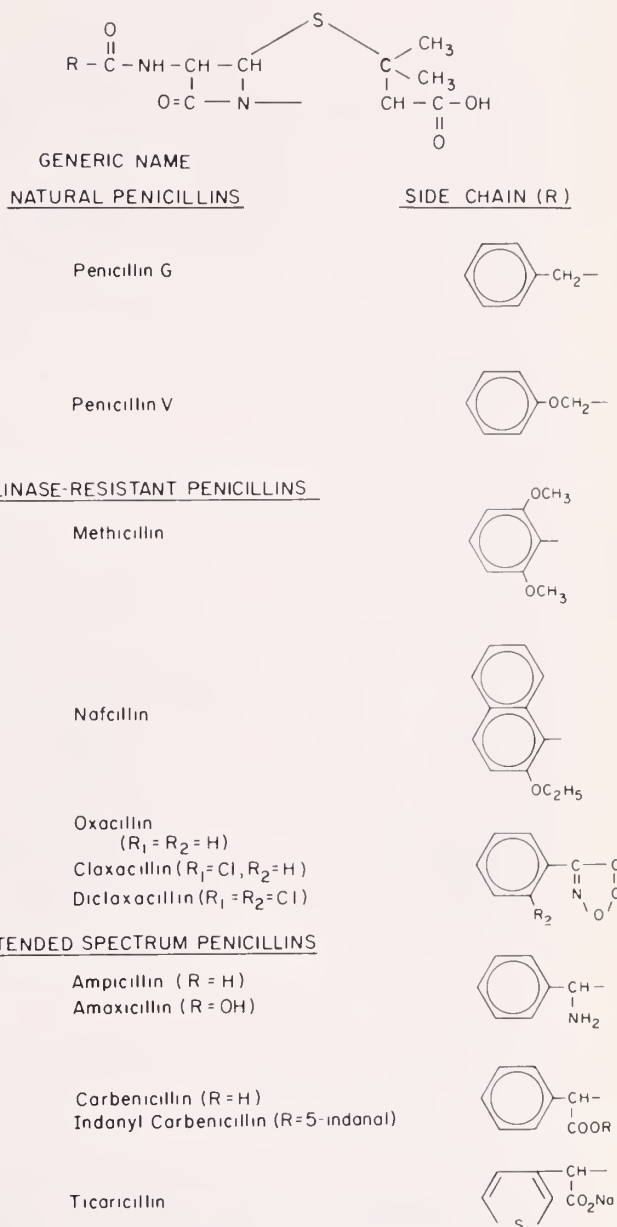


Fig. 1. Structural formulas for penicillins.

Although it might seem that bactericidal antibiotics such as the penicillins should be therapeutically superior to bacteriostatic agents (e.g., tetracyclines, chloramphenicol, sulfonamides), clinical proof of this is lacking except, perhaps, in the therapy of bacterial endocarditis.^{4,5}

RESISTANCE

A "resistant" organism is one that is not inhibited by levels of drug readily attainable in the serum. However, if massive doses of antibiotic are administered, or the infection lies in a site in which the

TABLE 1

Organism	ANTIMICROBIAL SPECTRUM OF THE PENICILLINS			
	"Natural" penicillins	Penicillinase-resistant	"Broad-spectrum" penicillins	
	Penicillin G Penicillin V	Methicillin Nafcillin Oxacillin Cloxacillin Dicloxacillin	Ampicillin Amoxicillin	Carbenicillin Ticarcillin
GRAM-POSITIVE COCCI				
Staph. aureus pen-sens	+++	+++	+++	+++
Staph. aureus pen-res	Resistant	+++	Resistant	Resistant
Staph. epidermidis	Variable	90% susceptible	Variable	Variable
Strep. pyogenes	+++	++	+++	+++
Pneumococcus	+++	++	+++	+++
Enterococcus	+	±	+	+
		Weakly inhibited		
GRAM-NEGATIVE COCCI				
Meningococcus	+++	+	+++	+++ (probably)
Gonococcus	+++	+	+++	++ (probably)
GRAM-POSITIVE RODS				
C. diphtheriae	+++	?	+++	?
Listeria	++	?	++	++
GRAM-NEGATIVE RODS				
H. Influenzae	+	±	++ (occ. resistant)	++
E. coli	Resistant	Resistant	++ (some resistant)	++
Klebsiella	Resistant	Resistant	Most Resistant	Resistant
Enterobacter	Resistant	Resistant	Resistant	++
Proteus mirabilis	+ / ++	Resistant	+++ (some resistant)	+++
Other proteus	Resistant	Resistant	Resistant	Variable
Pseudomonas	Resistant	Resistant	Resistant	++
Serratia	Resistant	Resistant	Resistant	Resistant
ANAEROBES				
Bacteroides fragilis	90% inhibited at high concentration	Weakly inhibited	90% inhibited at high concentration	60% inhibited at high concentration
Clostridia	+++	++	+++	+++
Anaerobic cocci	+++	++	+++	+++

+++ = highly susceptible

++ = moderately susceptible

+ = weakly susceptible

agent is concentrated (e.g., the urinary tract), ordinary susceptibility-testing may not be applicable. The level indicating resistance to carbenicillin and ticarcillin, drugs which are given parenterally in large doses, has been set about 100-fold higher than that for other penicillins.

The mechanisms of bacterial resistance to the penicillins fall into three major groups:^{1,6,7} (a) elaboration of substances (penicillinases) which inactivate the antibiotic; (b) alteration in the target site (cell-wall-forming enzymes) so that it no longer interacts with the drug; (c) impermeability of the bacterium so that the antibiotic cannot reach its target.

Organisms that elaborate penicillinases tend to be resistant to very high levels of antibiotic. The production of penicillinase by staphylococci is

controlled by an extra-chromosomal piece of DNA which is passed "horizontally" through the colony (phage transduction);¹ if a staphylococcus in a "closed-space" infection (e.g., bacterial endocarditis) is not initially resistant to penicillin G, it will not become so *in vivo*. Resistance to penicillin G connotes resistance to all of the congeners except the penicillinase-resistant ones. *Methicillin-resistant staphylococci*, widely prevalent in Europe but rare in North America at present, represent a special situation.⁸⁻¹¹ They are multiply drug-resistant organisms, often susceptible only to vancomycin. The mechanism of this resistance appears to be of the second kind noted above, in that these organisms exhibit a peculiarity of their cell wall structure.¹⁰

Resistance of Gram-negative bacilli to penicillins

is usually due to the production of penicillinases.¹ Among many of these organisms, including the recently recognized strains of ampicillin-resistant *Haemophilus influenzae*,¹²⁻¹⁴ production of this enzyme is mediated by R-factors (see Part I of this series on the tetracyclines), and is thus capable of being spread rapidly within a colony by sexual transfer (conjugation).^{15,16} R-factors often carry the information for resistance to many antibiotics, and may even be transmitted to different species of bacteria. Outbreaks of shigellosis due to strains resistant to various antibiotics are well documented, and multiply drug-resistant strains of *Pseudomonas*, *Klebsiella*, and other Gram-negative bacilli have been isolated. The potential dangers of such R-factor mediated resistance are clearly substantial.^{15,16}

The third mechanism is exemplified by the resistance of gonococci to penicillins. Though of low magnitude at present, the degree of resistance is rising progressively to the point where single-dose therapy of gonorrhea may no longer be possible. These organisms usually exhibit diminished susceptibility to a variety of antibiotics, presumably because they are relatively impermeable to these drugs.¹⁷

ANTIBACTERIAL SPECTRUM

The susceptibility patterns of various microorganisms to the penicillins are shown in Table I.¹⁸⁻³¹ Several "axioms" regarding the therapeutic use of these agents may be stated:

- (1) Bacteria inhibited by the "natural" penicillins (G,V) are usually more highly susceptible to these than to any other agent except possibly ampicillin or amoxicillin. Thus, penicillin G or V is the agent of choice for infections due to highly sensitive organisms.
- (2) The penicillinase-resistant penicillins are drugs of choice only for penicillin-resistant *Staphylococcus aureus*. At present, 60-80% of community staphylococci, and a higher proportion of hospital strains, exhibit such resistance.³²
- (3) Sensitivity patterns among Gram-negative bacilli vary from hospital to hospital and with time; thus, they are somewhat unpredictable.
- (4) Although most strains of *Staphylococcus epidermidis* (albus) are susceptible to penicillinase-resistant penicillins, about 10% are not.³⁰

Most anaerobic bacteria pathogenic for man are highly susceptible to all penicillins except for the penicillinase-resistant analogs. One exception is *Bacteroides fragilis*, of which 90% of strains are inhibited only by high levels of penicillin G (32 μ g/ml), and 60% by high levels of carbenicillin (128 μ g/ml).²⁶

The antibacterial activity of the two natural penicillins (G and V) is similar. In contrast, there are marked differences among the penicillinase-resis-

tant penicillins, methicillin displaying the least, and dicloxacillin the greatest activity *in vitro*.^{20,21} The spectrums of ampicillin and amoxicillin are similar, as are those of carbenicillin and ticarcillin; however, ticarcillin is several-fold more active against *Pseudomonas aeruginosa* than is carbenicillin.^{27,28}

COMBINATION WITH OTHER DRUGS

The penicillins are often given together with other antimicrobial agents. There are disadvantages to the use of combinations of antibiotics.²⁹ These include: (a) increased risk of adverse drug reaction; (b) possibly greater susceptibility to suprainfection (not proven); (c) drug antagonism. The last has been well demonstrated *in vitro* in a wide variety of settings,^{29,33} and is most typically seen when a bactericidal agent is combined with a bacteriostatic one. *In vivo* evidence of such antagonism has been less clear cut, but several examples are persuasive.^{29,34-36}

There are only a few instances in which a combination of a penicillin and another class of drug have proven synergistic. The most striking is in the therapy of enterococcal endocarditis with penicillin G and an aminoglycoside;²⁹ similar, though less impressive advantages of this combination have been claimed in endocarditis due to *Streptococcus viridans*.³⁷ The combination of carbenicillin and gentamicin exhibits synergism against the majority of strains of *Pseudomonas aeruginosa in vitro* and in animal studies,³⁸⁻⁴⁰ whether this applies in man as well is not clear.⁴⁰⁻⁴² *In vitro* data support the value of a combination of nafcillin or oxacillin together with gentamicin for serious disseminated staphylococcal infections (e.g., endocarditis),⁴³ and of penicillin G or ampicillin with gentamicin for *Listeria* infections;⁴⁴ however, *in vivo* data are lacking for these.⁴⁵

CLINICAL PHARMACOLOGY

Absorption

Some pertinent characteristics of the pharmacology of the penicillins in man, summarized in a recent review,⁴⁶ are shown in Tables 2 and 3. Of all the congeners, only penicillin V and amoxicillin regularly exhibit > 50% absorption by mouth.^{18,46-48} For reasons that are not clear, the potassium salt of penicillin V is better absorbed than the sodium salt.¹⁸ At least part of the relatively poor bioavailability of penicillin G, methicillin, carbenicillin, and nafcillin is due to their acid-lability.⁴⁹⁻⁵¹ Although carbenicillin itself is minimally absorbed by mouth, the indanyl ester is moderately well assimilated; after absorption it is promptly broken down to the parent compound.⁵¹ The presence of food in the stomach delays and impairs the absorption of most penicillins except penicillin V, ampicillin and amoxicillin; thus, it is prudent to advise patients to ingest penicillins 30-60 minutes before meals.

Serum Levels

The serum levels of various penicillins following

TABLE 2

PHARMACOLOGY OF THE PENICILLINS IN MAN (1)							
Penicillin	Oral Absorption (%)	Peak Serum Level ^a (μ g/ml)		Degree of Serum Protein-Binding ^a (%)	Percentage Penetration ^b		Metabolized (%)
		Total	Free		CSF Normal	CSF Inflamed	
<i>Natural penicillins</i>							
Penicillin G	15-30	1.5-2.7	0.6-1.0	60	0.5-2	2-6	19
Penicillin V	60	3-5	0.8	80	—	—	56
<i>Penicillinase-resistant penicillins</i>							
Methicillin	Minimal	—	—	40	0.8-5	3-12	8
Nafcillin	Variable, low	—	—	90	—	9	—
Oxacillin	33	5-6	0.6	90	< 6	—	49
Cloxacillin	49	7-14	0.6	93	—	—	22
Dicloxacillin	37	15-18	0.6	96	5 ^c	2 ^c	10
<i>Broad-spectrum penicillins</i>							
Ampicillin	30-50	2-6	1.6-5	20	4-5	36-40	12-20
Amoxicillin	74-80	7-8	6	20	—	—	28
Carbenicillin	Minimal	—	—	50	2-20	—	2
Indanyl carbenicillin	30	15	7.5	—	—	—	—

^aafter a 500 mg oral dose^bpeak level in cerebrospinal fluid $\times 100$

peak level in serum

^cdata for one patient only

a 500 mg oral dose are markedly dissimilar on account of differing degrees of absorption, metabolism and extent of serum protein-binding (Table 2).^{22,24,48,52-62} Because antibiotic bound to serum protein is neither antibacterially active nor readily available for diffusion into tissues, it is of interest to examine the levels of free drug in the serum after this same oral dosage (Table 2).^{50,51,55,56} The values are strikingly different from those for "total" (bound plus unbound) antibiotic and tend to vitiate many of the apparent differences among closely related congeners (e.g., oxacillin versus dicloxacillin).

Distribution

The penicillins are fairly well distributed into interstitial fluid, serosal cavities, synovial fluid and bone,⁴⁶ and the placenta.⁶³ Because they are relatively insoluble in lipid, they exhibit poor penetration into cells (including polymorphonuclear leukocytes) and across the blood-brain and blood-aqueous barriers.⁴⁶ Inflammation improves their traversal into the central nervous system and eye, both by reducing the normal barriers and by impairing the activity of the organic anion pumps in the choroid plexus (brain) and ciliary body (eye).^{64,65} Data for meningeal penetration shown in Table 2 should be regarded circumspectly as they were gathered from small numbers of subjects under markedly varying conditions. In treating meningitis, the physician should not decrease the dosage of penicillin as the disease improves because the permeability of the blood-brain barrier declines during convalescence. Although the issue is not firmly settled, the penicillins seem to penetrate young abscesses fairly well,^{46,66,67} and it may well be that some phenomenon other than accessibility to drug

TABLE 3

PHARMACOLOGY OF THE PENICILLINS IN MAN (2)			
Penicillin	HALF-LIFE (hr)		
	Normal	Anuric	Hemodialysability
<i>Natural penicillins</i>			
Penicillin G	0.7	6-10	30-50 ml/min $t_{1/2}$ decreased by 45%
<i>Penicillinase-resistant penicillins</i>			
Methicillin	0.43	4	No
Nafcillin	0.5-1.0	1.2	No
Oxacillin	0.4-0.7	0.5-1.0	No
Cloxacillin	0.5	0.8	No
Dicloxacillin	0.8	1-1.5	No
<i>Broad-spectrum penicillins</i>			
Ampicillin	1-1.3	8-20	$t_{1/2}$ decreased by 75%
Amoxicillin	1-1.3	—	—
Carbenicillin	1	10-20	$t_{1/2}$ decreased by 60-70%

is responsible for the failure of antimicrobial agents to sterilize such foci.

Elimination

The major route of elimination of most penicillins is in the urine as unchanged drug; thus, all of the congeners produce high urinary concentrations if they are absorbed. A portion of each agent is metabolized (Table 2);^{46,59} this is especially noteworthy with penicillin V and oxacillin, and contributes to the minimal change in half-life of oxacillin in renal failure. Most penicillins are actively secreted into the bile, producing biliary concentrations which exceed those in serum; however, the transport mechanisms are easily saturated, particularly by oxacillin and carbenicillin. Levels of penicillin G

and ampicillin in bile range up to ten times those in serum, and the ratio is still higher for nafcillin (40:1 to 400:1).⁴⁶ Penetration into the bile is extremely poor in the presence of common duct obstruction. Despite the presence of active secretion, the only congener for which biliary secretion plays an important role in elimination is nafcillin.⁶⁸

Because most penicillins are rapidly secreted into the urine, their half-lives in the serum are exceedingly short (Table 3).^{58,69,70} Correspondingly, renal failure imposes a great hindrance upon elimination mechanisms, prolonging the half-life substantially.^{49,69,71-76} Nafcillin, oxacillin, cloxacillin and dicloxacillin constitute exceptions to this general rule because of their more extensive metabolism and/or biliary secretion. Recently, a nomogram has been published for the adjustment of dosages of penicillin G in patients with renal impairment.⁷⁵ In the presence of complete anuria, it is generally inadvisable to exceed 3 million units of penicillin G per day; with coexisting advanced liver disease, this dosage should be halved. Those agents which exhibit the greatest prolongation of half-life in renal failure are (with the exception of methicillin) most easily hemodialyzed (Table 3).^{71,72,74-78} None of the penicillins is readily removed by peritoneal dialysis.

The effects of combined hepatic and renal impairment on the elimination of the penicillins have not been well defined. In general, the superimposition of liver disease appears to prolong the half-life over that found in renal impairment by several-fold.^{68,70-72,74,75} for nafcillin, the difference may be substantial. Limitations of space preclude discussion of the effects of probenecid on the excretion and distribution of penicillins; these have been reviewed recently.⁴⁶

Although not shown in the tables, the pharmacokinetics of flucloxacillin and ticarcillin resemble those of dicloxacillin and carbenicillin, respectively.^{27,28,55,61,62,76} The repository forms of penicillin G include procaine penicillin G and benzathine penicillin G; these are absorbed from intramuscular sites much more slowly than are the sodium or potassium salts, but after absorption, they exhibit the kinetics of penicillin G. Antibiotic is detectable in the serum for a prolonged period (12-24 hours) after intramuscular injection of procaine penicillin G, but the peak level following a dose of 600,000 units is only 1-3 $\mu\text{g/ml}$ which is similar to the level produced by ingestion of potassium penicillin V 500 mg.^{18,54,79}

ADVERSE EFFECTS OF THE PENICILLINS

The major adverse effect of the penicillins, hypersensitivity reactions, ranges in clinical severity from mild rash (\pm eosinophilia) through serum sickness to immediate anaphylaxis and death.⁸⁰⁻⁸³ We have sometimes continued to treat patients with rash and eosinophilia when such therapy was warranted (e.g., enterococcal endocarditis). Although all of the penicillins are capable of producing hyper-

sensitivity reactions, rashes appear to be more common with ampicillin than with other congeners (7% versus 3%).⁸³ An ill-understood skin reaction to ampicillin is almost universal among patients who have infectious mononucleosis or cytomegalovirus infection.⁸¹ Many individuals relate a history of penicillin allergy, but manifest none on re-exposure to the drug years later. In some instances, this may be due to the development of blocking antibodies.⁸³

Skin testing with penicillins is not an accurate way to predict anaphylaxis, apparently because conjugated metabolites, rather than the parent substance, are responsible for many of the reactions.⁸³ The use of penicillin derivatives (penicilloyl polylysine and minor determinant mixture) appears to correlate well with penicillin allergy,⁸² and these preparations have recently become commercially available. It is preferable not to administer penicillins at all to individuals with a history of penicillin-related anaphylaxis or giant urticaria. Clinical cross-reactivity to cephalosporins occurs in only about 8-10% of penicillin-allergic individuals;⁸⁵ we have avoided cephalosporins in patients with penicillin-related anaphylaxis or giant hives, but not in those with milder reactions.

Other reactions have been noted with the various penicillins. Although it seems reasonable to expect that any of the penicillins might produce these, some have been observed with only one or two agents. Some examples are:

- (1) Coombs' positivity is noted in some recipients of penicillins; hemolytic anemia, however, is rarely seen.^{84,85}
- (2) Selective or pancytopenia — various penicillins.⁸⁶
- (3) Hepatitis — oxacillin, carbenicillin.⁸⁷
- (4) Nephritis — appears to be most common with methicillin. Usually interstitial nephritis, often with fever, eosinophilia and an abnormal urinary sediment.⁸⁸⁻⁹⁰ Glomerular and tubular damage have rarely been noted.
- (5) Systemic vasculitis.
- (6) Bleeding tendency due to platelet dysfunction⁹¹ — carbenicillin.
- (7) Diarrhea — common with ampicillin and penicillinase-resistant congeners as well as indanyl carbenicillin in high dosage; questionably less frequent with amoxicillin than ampicillin.
- (8) Glossitis, stomatitis.
- (9) Convulsions — penicillin G or carbenicillin. Usually associated with high dosage in individuals with renal impairment; often some underlying seizure focus is present.⁹²
- (10) Central nervous system reactions (other than seizures) have been noted in some recipients of procaine penicillin G, apparently due to rapid absorption of procaine.⁹³
- (11) Pain and inflammation at injection sites (phlebitis, sterile intramuscular abscesses).
- (12) Suprainfection (1% of recipients).⁷⁹

TABLE 4

TYPICAL DOSAGES OF PENICILLINS

Agent	Oral Dosage	Cost of One Day's Oral Therapy with 500 mg Doses ^a (\$)		Intravenous Dosage ^b
		Tradename	Generic	
Penicillin G	250-500 mg four times a day	Tradename	0.46	Up to 40 million units per day (rarely may give more)
		Generic	0.18	
Penicillin V	250-500 mg four times a day	Tradename	0.67	—
		Generic	0.23	
Methicillin	—	—	—	8-12 g per day (eg, 2 g every 4 hours)
Nafcillin	—	—	—	8-12 g per day (eg, 2 g every 4 hours)
Oxacillin	250-500 mg four times a day	Tradename	1.39	8-12 g per day (eg, 2 g every 4 hours)
Cloxacillin	250-500 mg four times a day	Tradename	1.52	—
Dicloxacillin	250-500 mg four times a day	Tradename	1.85	—
Ampicillin	250-500 mg four times a day	Tradename	1.01	8-12 g per day (eg, 2 g every 4 hours)
		Generic	0.53	
Amoxicillin	250-500 mg three times a day	Tradename	1.75	—
Carbenicillin	—	—	—	24-36 g per day (eg, 2-3 g every 2 hours)
Indanyl carbenicillin	500 mg four times a day	Tradename	1.51	—
Ticarcillin	—	—	—	24-36 g per day (eg, 2-3 g every 2 hours)

^aAverage wholesale prices of trademark and generic name products

^bDosage in adult patients with serious infections and normal renal function

- (13) Hyperkalemia with potassium penicillin G (contains 1.7 mEq potassium ion per 1 million units) and an excessive sodium load with carbenicillin (contains 4.7 mEq sodium ion per gram of antibiotic).

- (14) Hypokalemia — penicillin G, carbenicillin.⁹⁴

The first five reactions appear to be hypersensitivity reactions.

THERAPEUTIC USE

The penicillins are drugs of choice for infections due to organisms listed in Table 1 that are highly or moderately susceptible. They are also preferred therapy for anthrax, erysiploid, salmonellosis, shigellosis, actinomycosis, rat-bite fever, syphilis, leptospirosis, one form of borreliosis, and infections due to *Pasteurella multocida*. Because of the emergence of ampicillin-resistant *Haemophilus influenzae*,⁹⁵ it is now common practice to administer chloramphenicol together with penicillin G or ampicillin for meningitis in children until definitive identification and susceptibility testing of the infecting organism can be done. Carbenicillin, which is relatively resistant to the beta-lactamase produced by these strains, is being studied as a therapeutic alternative.

Serious enterococcal infections such as endocarditis should be treated with penicillin G or ampicillin together with streptomycin or gentamicin. A penicillin alone should not be used for potentially dangerous illnesses due to Gram-negative bacilli (enterobacteriaceae) until their susceptibility has been established; *Pseudomonas* bacteremia in the compromised host may best be treated with a combination of carbenicillin and gentamicin⁴⁰ or ticarcillin and tobramycin. Although carbenicillin appears

to be effective therapy for infections in which *Bacteroides fragilis* is present,⁹⁶ controlled comparisons with other agents have not been carried out. We regard clindamycin as a drug of choice for infections due to predominantly to this organism, with chloramphenicol, metronidazole or carbenicillin as second choice.

The ideal chemotherapeutic approach to mixed aerobic and anaerobic infections of the abdomen (e.g., peritonitis) and pelvis remains unsettled in this author's opinion. In one randomized study of patients with penetrating abdominal trauma, the frequency of anaerobic infections (mainly *Bacteroides fragilis*) was markedly less with clindamycin and kanamycin than with cephalothin and kanamycin.⁹⁷ High doses of penicillin G given parenterally produce serum levels sufficient to inhibit 90% of strains of *Bacteroides fragilis*;^{26,98} in contrast, only 40% of strains are inhibited by comparable doses of cephalothin.⁹⁹⁻¹⁰¹ Thus, it is possible that penicillin G would prove as efficacious as clindamycin when combined with an aminoglycoside. In the absence of a controlled clinical comparison of these regimens, we have tended to use clindamycin with gentamicin in the treatment of peritonitis and mixed pelvic infection (excluding the gonococcus).

Table 4 contains a list of suggested dosages of the penicillins for oral and intravenous administration, while regimens for the treatment of selected infections are shown in Table 5.¹⁰²⁻¹⁰⁵

PROPHYLACTIC USE

The efficacy of the penicillins in prevention of reoccurrences of rheumatic fever is indisputable; benzathine penicillin G (1.2 million units intramus-

TABLE 5

PENICILLIN THERAPY OF SELECTED INFECTIONS

Disease	Therapy with Penicillins ^a	Alternative
Pneumococcal pneumonia	Penicillin G 2-4 million units intravenously per day for 5-7 days ¹⁰²	Cephalosporin Erythromycin
Pneumococcal meningitis	Penicillin G 2 million units intravenously every 2 hours for 2 weeks	Chloramphenicol Erythromycin
Streptococcal pharyngitis	Penicillin G or V 250 mg orally four times a day or procaine penicillin G 600,000 units intramuscularly daily for 10 days	Erythromycin Clindamycin
<i>Streptococcal viridans</i> endocarditis	Penicillin G 8-20 million units intravenously per day for 4 weeks (some authors advocate addition of streptomycin for first 2 weeks ¹⁰³)	Cephalosporin Erythromycin
Enterococcal endocarditis	Penicillin G 20-30 million units or ampicillin 12 g intravenously per day and streptomycin (or, if streptomycin not synergistic, gentamicin) parenterally for 4 weeks	Vancomycin Erythromycin
Meningococcal meningitis or bacteremia	Penicillin G 2 million units intravenously every 2 hours for 10-14 days	Chloramphenicol Erythromycin
Gonorrhea		
Uncomplicated genital	Aqueous procaine penicillin G 4.8 million units intramuscularly (two sites) + 1 g probenecid by mouth; or ampicillin 3.5 g by mouth + probenecid (For alternative drugs, dosage, and duration, see reference 104.) Recently, there have been reports of strains highly resistant to penicillins. Streptomycin is a drug of choice for these strains.	Tetracycline (not in pregnancy) Spectinomycin (? not in pregnancy) Erythromycin Cefazolin
Acute salpingitis	See reference 104; requires higher doses than uncomplicated genital disease	
Chronic pelvic inflammatory disease		
Diphtheria	Antitoxin therapy definitive; penicillin G 2-3 million units intravenously per day or procaine penicillin G 600,000 units intramuscularly daily for 10-14 days to eliminate carriage of organism	Erythromycin Clindamycin
Gas gangrene (clostridial)	Penicillin G 20-30 million units intravenously per day	Cephalosporins Clindamycin
<i>Listeria</i> bacteremia and/or meningitis	Penicillin G 2 million units intravenously every 2 hours for 2 weeks (An aminoglycoside may be synergistic.)	
Shigellosis	Ampicillin 500 mg by mouth every 6 hours	Depends on sensitivity
Typhoid fever	Chloramphenicol is traditional drug of choice, though recent data indicate amoxicillin, 1 g by mouth every 6 hours is equally good	
Aspiration pneumonia and lung abscess; oropharyngeal anaerobic infection	Penicillin G 4-8 million units intravenously per day for 2 weeks (pneumonia) to 6 weeks (lung abscess) ¹⁰⁵	Cephalosporin Clindamycin
<i>Haemophilus influenzae</i> meningitis	Treat with ampicillin (400 mg/kg parenterally per day) for 10-14 days; include chloramphenicol initially until susceptibility to ampicillin demonstrated	

^aPenicillin G can be replaced by ampicillin, but not reliably by other penicillins.

cularly monthly) appears to be superior to oral regimens, possibly because doses are missed with the latter.¹⁰⁶ In contrast, the value of penicillin therapy in preventing glomerulonephritis¹⁰⁷ or rheumatic fever after streptococcal infection is established remains controversial.

For reliable prophylaxis against gonorrhea after sexual exposure, it is probably best to administer therapy in the same manner as for uncomplicated clinical disease (Table 5). This regimen is also adequate for the treatment of incubating syphilis if given within 24 hours after sexual contact; thereafter, 2.4 million units of benzathine penicillin G intramuscularly provides more dependable therapy.

The problems of prophylaxis of bacterial endocarditis in patients with valvular heart disease have been reviewed recently by Kaye.¹⁰⁸ Although the value of such prophylaxis has not been proven, it is generally, and properly, advocated. Patients with a predisposing cardiac lesion should be informed of the kinds of procedures which carry a high risk, e.g. dental manipulation, genitourinary instrumentation, and abdominal surgery. The current American

Heart Association guidelines for prophylaxis, shown in Tables 6 and 7, are based on the assumption that *Streptococcus viridans* presents the major threat after oropharyngeal procedures, and the enterococcus after genitourinary and abdominal manipulations.

CHOICE OF A PENICILLIN

The choices in penicillin therapy are less extensive than may appear from an initial perusal of the array of agents available. The physician must first consider which class of penicillin is indicated. For the treatment of infections susceptible to penicillin G, no other congener is more effective, although ampicillin and amoxicillin are as effective. (Carbenicillin in high dosage is likely to be successful as well.) If an oral drug is to be used, potassium penicillin V produces more reliable blood levels and is, therefore, slightly preferred over penicillin G.

The only indications for penicillinase-resistant penicillins are the suspected or demonstrated presence of *Staphylococcus aureus*. Since 60-80% of community, and a higher proportion of hospital

TABLE 6

REGIMENS RECOMMENDED BY AMERICAN HEART ASSOCIATION
FOR PROPHYLAXIS FOR DENTAL PROCEDURES^a

Penicillin

Intramuscular:

600,000 units of procaine penicillin G mixed with 200,000 units of crystalline penicillin G 1 hour prior to procedure and once daily for 2 days following procedure.

OR

Oral:

500 mg penicillin V or phenethicillin 1 hour prior to procedure and then 250 mg every 6 hours for remainder of that day and for 2 days following procedure.

OR

Oral:

1,200,000 units of penicillin G 1 hour prior to procedure and then 600,000 units every 6 hours for remainder of that day and for 2 days following procedure.

In patients allergic to penicillin or receiving continual oral penicillin for prophylaxis against rheumatic fever, who may harbor penicillin-resistant viridans-type streptococci:

Oral:

500 mg of erythromycin in adults (200 mg/kg in small children) 1½ to 2 hours before procedure and then 250 mg every 6 hours (10 mg/kg in small children) for remainder of that day and for 2 days following procedure.

^afrom reference 108

strains of this organism currently produce penicillinase, a member of this group or a cephalosporin should be used in the initial therapy of staphylococcal infections until the sensitivity of the organism has been determined. The penicillinase-resistant penicillins will "cover" mild to moderate streptococcal and pneumococcal infections as well as ones due to anaerobes other than *Bacteroides fragilis* (intestinal) or clostridia. In high dosage, they also have some activity against *Haemophilus influenzae* and, combined with gentamicin, against enterococci.¹⁰⁹ This knowledge may help the physician to avoid adding a second penicillin pending identification of the infecting organism. In certain rare circumstances, however, it may be desirable to add another penicillin, usually penicillin G or ampicillin. There is little to choose among oxacillin, cloxacillin, dicloxacillin or flucloxacillin by the oral route, or among oxacillin, dicloxacillin, nafcillin or methicillin parenterally. Comparative studies have shown no important difference in therapeutic effect.^{21,88,110} The marked acid-lability of methicillin could affect its stability in many intravenous solutions; in addition, this analog appears to produce interstitial nephritis more commonly than others.⁸⁸ For these reasons, we rarely use methicillin.

Ampicillin is especially useful for infections due to *Haemophilus influenzae* and *Escherichia coli*, and it may be more efficacious than penicillin G for serious disease due to the enterococcus and *Listeria monocytogenes*.¹¹¹ It is as useful as other agents in the treatment of uncomplicated *Escherichia coli* urinary tract infections, and for exacerbations of chronic bronchitis (see Part I of this series on the tetracyclines). It is generally effective for salmonellosis and shigellosis, though it should not be used for simple salmonella gastroenteritis.¹¹² Although amoxicillin produces twice the serum antibacterial

TABLE 7

REGIMENS RECOMMENDED BY AMERICAN HEART ASSOCIATION
FOR PROPHYLAXIS FOR GASTROINTESTINAL AND GENITOURINARY
TRACT SURGERY AND INSTRUMENTATION^a

For most patients:

600,000 units of procaine penicillin G mixed with 200,000 units of crystalline penicillin G intramuscularly 1 hour prior to procedure and once daily for 2 days following procedure plus streptomycin, 1-2 g intramuscularly, 1 hour prior to procedure and once daily for 2 days following procedure.

In children, daily dose of streptomycin is 40 mg/kg (not to exceed 1 g/24 hours).

OR

25-50 mg/kg ampicillin orally or intravenously 1 hour before procedure and then 25 mg/kg every 6 hours for that day and for next 2 days plus streptomycin as above.

For patients allergic to penicillin:

Erythromycin as in Table 6 plus streptomycin as above.

OR

Vancomycin, 0.5-1.0 g intravenously (20 mg/kg in children) 1 hour prior to procedure and then 0.5 g intravenously (10 mg/kg in children) every 6 hours for 72 hours plus streptomycin as above.

^afrom reference 108

activity of ampicillin after equivalent oral doses, the only evidence of a therapeutic advantage is in the oral therapy of typhoid fever.^{113,114} The drug may be inferior to ampicillin for shigellosis,¹¹⁵ and is more expensive than the latter. Amoxicillin has been alleged to produce less diarrhea than ampicillin, especially as the pediatric suspension, but controlled data are not convincing.

Carbenicillin and ticarcillin exhibit activity unique among the penicillins. They are efficacious in the treatment of systemic infections due to Gram-negative bacilli (except *Klebsiella*). The only apparent advantage of ticarcillin over carbenicillin lies in its greater activity against *Pseudomonas in vitro*.^{27,28} Whether this will be translated into a clinical advantage remains to be seen. The oral preparation of carbenicillin (indanyl carbenicillin) produces relatively low serum levels of drug, and is useful mainly in the treatment of urinary tract infections. Because sporadic urinary tract infections usually respond to much less expensive traditional agents, while complicated ones involving obstruction or indwelling catheters generally relapse promptly after (or during) therapy with indanyl carbenicillin, the number of instances in which this agent is of value is limited.

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THERE ARE A LOT OF PEOPLE GETTING BETWEEN YOU AND YOUR PATIENT.

Medicine today is in the spotlight, subjected to all kinds of scrutiny. Your control over patient therapy is being monitored, judged and occasionally abrogated, sometimes by unknown third parties.

The worry is that in the wake of this focus, the relationship between you and your patient will be weakened, without offsetting benefits. Consider three examples:

Drug substitution In most states, pharmacy laws, regulations or professional custom stipulate that your non-generic prescriptions be filled with the precise products you prescribe. But in the last five years, a dozen or more State laws have been changed, permitting the pharmacist in most cases to select a product of the same generic drug to fill any prescription.

Ironically, this dilution of physician control has taken place against a background of growing evidence that purportedly equivalent drug products may be inequivalent, since neither present drug standards nor their enforcement are optimal. In fact, the FDA itself says it has not enforced the same standards for hundreds of "follow-on" products that it had applied to the original NDA approvals. Thus physician control over patient therapy is being eroded with a risk that patients may be exposed to drugs of uncertain quality.

The major advertised claim for substitution is reduced prescription prices for consumers. Yet no documentation of any significant savings has been produced.

MAC Maximum Allowable Cost, MAC for short, is a Federal regulation designed to cut the Government's drug bill by setting price ceilings for drugs dispensed to Medicare and Medicaid patients. Unless the prescriber certifies on the prescription that a particular product is medically necessary, the Government intends to pay only for the cost of the lowest-priced, purportedly-equivalent,

generally-available product. The effect of the program may be that elderly and indigent patients will be restricted to products which someone in Washington believes are priced right. Practicing doctors will have little to say about administration of the program, since Government will have absolute authority to make its choices stick.

The drug lag The future of drug and device research depends upon a scientific and regulatory environment that encourages therapeutic innovations. The American pharmaceutical industry annually is spending more than \$1 billion of its own funds and evaluating more than 1,200 investigational compounds in clinical research. Disease targets include cancer, atherosclerosis, viruses and central nervous system disorders, among others. But there is a major barrier to the flow of new drugs to your patients: The cost of the research is more than ten times what it was, per product, in 1962; and whereas governmental clearance of new drug applications took six months then, it commonly consumes two years now.

The FDA needs adequate time, of course, to consider data. But it is equally clear that the present approval process contributes to needless delay of needed therapy. That's why the increased efficiency of the drug approval process is vital to all our futures.

If these issues concern you, we suggest that you make your voice heard—among your colleagues and your representatives in State legislatures and in Washington.

It could make a difference in your practice tomorrow.



Pharmaceutical Manufacturers Association
1155 Fifteenth Street, N.W., Washington, D.C. 20005



Maine Blue Cross and Blue Shield News

BLUE SHIELD CLAIMS PROCESSING: STILL WORKING OUT THE PROBLEMS

While strides have been made in "de-bugging" the new automated Blue Shield claims systems, problems still exist that need to be resolved.

There is still a certain error level being experienced in the system with both the input from physicians and within the system at Maine Blue Cross and Blue Shield. Both problems are to be expected with a transition to automation, but both should also be clearing up by now.

To help with the input, we ask you to make sure that the data on the claim form is accurate and that you use the new one-sheet claim form. Please double-check the following areas:

- A. Dates of admission and discharge are required on claims for inpatient hospital medical care.
- B. The patient's Date of Birth (not age) is required in Item #2.
- C. The Blue Shield assigned Physician Code Number should be entered in Item #31.
- D. The place of service codes to be used in Item #24B are:
 - 1. In-Patient
 - 2. Out-Patient
 - 3. Office
 - 4. Home

We will make every effort to ensure that the data from your claim forms is recorded properly in the system.

In the same vein, if you find that the time lag between the date you submit a claim and the date you receive reimbursement is more than a month, please contact Professional Relations and we will try to hasten the payment process for you.

Questions have also been raised about the single claim form. It was designed to accommodate the automated system wherein a computer print-out of all claims payments is submitted to you, and a *Health Care Benefits Summary* is sent to subscribers, thereby eliminating the need for additional claim copies. If you require additional copies for your office, feel free to use as many claim sheets per patient as you need.

The single sheet claim form is also compatible nationally with a uniform claim concept that could be used universally, thus making claims preparation easier in the long-run within the doctor's office.

The new "Health Care Benefits Summary" replaces the subscriber's pink copy of the old Blue Shield claim form.

This new form was developed to cut postage and mailing costs, by summarizing, on one form, all of the forms which have been submitted to Blue Shield during a period of illness or hospitalization. Eventually, as the Blue Cross system becomes automated, all hospital charges will also appear on the *Benefits Summary*, resulting in an even greater cost savings.

Please let Professional Relations know if you need any further explanation or help with the new claim system. You may use our toll-free number 1-800-482-0740.

Maine Medical Association

SPECIAL COMMITTEES — 1976-1977

Special Committees for 1976-1977 as appointed by the President of the Maine Medical Association, Richard C. Leck, M.D., of Bath.

Ad Hoc Committee on Alcoholism

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Frederick S. Larned, M.D., 155 Spurwink Ave., Cape Elizabeth 04107
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Necrology

JAMES PATTERSON, M.D.

1880-1976

Dr. James Patterson, 96, of Portland, Maine, died on May 20, 1976.

Born in Scotland on March 16, 1880, he was the son of James and Janet H. Patterson.

He was graduated from the University of Chicago in 1905 and received his medical degree from Rush Medical College in 1911. Dr. Patterson interned at the Presbyterian Hospital in Chicago

and held hospital appointments there and at the White Plains Hospital in New York before locating in Maine in 1940.

An honorary member of the Cumberland County Medical Society and the Maine Medical Association, he received a 50-year pin in 1961, a 55-year pin in 1966, a 60-year pin in 1971 and would have been eligible for his 65-year pin at the June 1976 annual session.

News, Notes and Announcements

Long Course on Recent Advances in Pulmonary Pathology

A comprehensive program on Recent Advances in Pulmonary Pathology will be given by a faculty of 14 authorities at the Annual Meeting of the U.S.-Canadian Division of the International Academy of Pathology in Toronto, Ontario, Canada. The course will be given Thursday, March 17, 1977, at the Sheraton Centre Hotel.

Course Director: Dr. William M. Thurlbeck, Professor and Head, Department of Pathology, The University of Manitoba, 770 Bannatyne Avenue, Winnipeg, Manitoba, Canada R3E OW3.

Further information may be obtained from Dr. Leland D. Stoddard, Secretary-Treasurer, U.S.-Canadian Division, International Academy of Pathology, Department of Pathology, Medical College of Georgia, Augusta, Georgia 30902. Telephone (404) 724-2973.

The Fortieth Annual New Orleans Graduate Medical Assembly March 28, 1977 Through March 31, 1977 The Fairmont, New Orleans, Louisiana

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Letter to the Editor

To the Editor:

As the Commander of the largest military health care delivery system in the New England states, I am writing your society to introduce your physicians to a unique form of practice ... Army Medicine. The elimination of the Physician Draft has caused many physicians to view an experience in military medicine as a totally voluntary opportunity. We believe that we can offer today's physician an extremely attractive professional and social alternative to private practice.

Here at Cutler Army Hospital, Fort Devens, Massachusetts, there are a number of physician vacancies in internal medicine, general medicine, pediatrics and anesthesia. We offer today's

physician an environment in which he or she can pursue the practice of pure medicine as other health professionals manage the administrative tasks. Today's Army Medical Department offers guaranteed assignments for physicians and a competitive salary with numerous benefits.

Physicians who are interested in obtaining information pertinent to a medical practice at Fort Devens are encouraged to contact CPT Peter D. Tremblay, Personnel Procurement Office, (617) 796-2004. Through CPT Tremblay, a tour of our facilities as well as a meeting with Army physicians can be arranged.

EUGENE P. HYLAND, M.D.
Colonel, MC
Commanding

County Society Notes

Penobscot

The annual meeting of the Penobscot County Medical Society was held on May 18, 1976 at Sing's Restaurant in Bangor, Maine.

The meeting was opened by the President, Dr. Thornton W. Merriam, Jr. and the minutes of the previous meeting were read and approved. Dr. David S. Beebe presented the report of the Treasury. This revealed the organization to be financially solvent.

Dr. Robert P. Andrews moved, and it was seconded, that the Executive Committee consider the subject of dues and the amount thereof as is reflected in excess funds from the Treasury.

There was no old business.

Under the heading of Committee Reports, a report of the recent House of Delegates meeting was presented. It was announced that Dr. Richard T. Chamberlin was to be hired as the Assistant Executive Director of the Maine Medical Association. It was also announced that approximately 70 percent of the membership of the Maine Medical Association has reported their continuing medical education hours. The proposed budget for the 1976-1977 year was reviewed. It was noted that *The Journal of the Maine Medical Association* was to be continued. Nominees for officers of the Maine Medical Association for the year 1976-1977 were also presented. Following this report, the various resolutions to be presented at the annual meeting of the Maine Medical Association were presented and voted upon by our Society in order to instruct the delegates how to vote on the issues. Resolutions by the Maine Medical Association Executive Committee that "resolved that discontinuation of Association member shall terminate concomitantly such component Society membership." This was approved in favor. Second resolution also from the Maine Medical Association Executive Committee stated "resolved that any member suspended for non-payment of dues must satisfy all debts to the Association including unpaid dues before reinstatement or re-election to membership." Voted in favor. The Aroostook County resolution stating "resolved that the Executive Committee of the Maine Medical Association begin a legislative action which would allow any Maine physician to have the option of billing patients directly or accepting assignment under the Medicaid Program." This was defeated.

A report of the Executive Committee of the Maine Medical Association was presented by Dr. Merriam. This included the following. A request that the Aroostook County Medical Society review whether any action should be taken against Dr. Yap because of his recent court conviction. Dr. Richard A. Gaillard reported that the PSRO group of the otorhinolaryngology Society has been requested to investigate the matter. Secondly, to investigate the swine flu immunization program. Dr. Denny-Brown has been appointed to this committee. Lastly, with regard to the Blue Cross-Blue Shield Coverage Contract, it was advised that each physician check to see whether or not the old major medical coverage could be reinstated at age 65 if it is dropped now. It was also reported that the Section of Otorhinolaryngology would present a resolution to the House of Delegates stating "resolved that the Maine Medical Association rename the Section of Otorhinolaryngology to the Section of Otorhinolaryngology and Maxillo-facial Surgery. This was voted in favor by the Society. Lastly, the Cumberland County resolution to be presented to the House of Delegates states that "resolved that the Maine Medical Association adopt a policy requiring a minimum of 150 hours over a three-year period of continuing medical education in order to maintain membership in the Maine Medical Association." This was voted in favor by the Society.

It was announced that representatives of the Penobscot County Medical Society, Eastern Maine Medical Center, St. Josephs Hospital, and the Bangor Daily News recently met together to explore ways in which to promote better communication between the news media and the medical profession. It was felt that the County Medical Society should form a committee whose function would be to serve as this liaison with the news media. A motion was made, and it was seconded and passed, that the president appoint such a committee.

Dr. A. Dewey Richards discussed a proposal from the State of Maine which has requested that the Health Care Financing Committee of the Maine Medical Association propose a State-wide fee schedule. This proposal is being investigated and will be discussed at the annual meeting of the Maine Medical Association.

Application for membership to the Penobscot County Medical Society was received from Dr. Angela C. Gilladoga. This application after review, was approved.

The Nominating Committee presented the following slate of officers for the Penobscot County Medical Society for the year 1976-1977:

President: Dr. John A. Woodcock, Bangor

President-elect: Dr. Philip G. Hunter, Bangor

Secretary: Dr. H. Clement Jurgeleit, Bangor

Treasurer: Dr. A. Marshall Smith, Bangor

Counsellor for three years: Dr. John C. Schroder, Bangor

As there was no further business, the meeting was adjourned.

PHILIP G. HUNTER, M.D., *Secretary*

York

A special meeting of the York County Medical Society was called by our President, Dr. Owen O. Dow, at the request of the members who attended the May meeting at the Webber Hospital. This former meeting was also held at the Webber Hospital on September 15, 1976.

The program consisted of a Social Hour from 7:00 to 8:00 p.m. There was no dinner. Following the social hour, an interesting meeting on "Malpractice" (Informed Consent) was presented by Dr. James H. Bonney of Portland, Maine, who is both a physician and a lawyer. It was videotaped and simulated a courtroom atmosphere. One week prior to this meeting, each member of the York County Medical Society was sent a simulated case situation and face sheet which was used at a prior meeting at the Maine Medical Center, for their perusal. Comments by Dr. Bonney and questions and answers were interspersed with this videotape presentation. All and all, it was an outstanding program. We are sorry that more members did not take advantage of it. Twenty-one physicians attended and all of these were very well satisfied.

MELVIN BACON, M.D., *Secretary*

Kennebec

The Kennebec County Medical Association met at the Holiday Inn in Augusta, Maine on September 16, 1976, with 29 members and one guest in attendance.

Following the cocktail hour, a very nice meal was enjoyed. Minutes of the previous meeting were approved.

Correspondence from the Maine Medical Association regarding Honorary membership of Dr. Guite; Affiliate membership of Drs. Hurwitz, Reel and Wilson; and Senior membership of Drs. Towne, Emanuel and Simpson were read.

Applications for membership were read for the first time from Drs. Anton Braun, Stephen Eccher, Daniel Clarke and Henry Ryan.

There being no further business, the program was turned over to Mr. Charles T. Zurhorst, a semi-retired public relations consultant, now residing in Machias, Maine, who discussed with the members of the Association the factors relating to the physician's image in the community and what the various things were that could be done to improve the image of the physician. The discussion was interesting to the members, and I expect, that in the future some of Mr. Zurhorst's suggestions would prove fruitful.

O. THOMAS FEAGIN, M.D., *Secretary*

Lincoln-Sagadahoc

The regular monthly meeting of the Lincoln-Sagadahoc County Medical Society was held at The Ledges in Wiscasset, Maine on September 21, 1976. Twenty-seven members and two

guests were present.

The minutes of the June meeting were accepted.

The Board of Censors proposed Dr. Edward C. Schmidt for active membership; the application was accepted unanimously.

Dr. Elihu York reported that a group must recruit 2,000 victims to qualify for a gun for inoculation clinics; one would be available for this area for Swine Flu, October 28-31.

Dr. Robert M. Hassan reopened discussion of unified membership. The general consensus was that that subject had received worthy debate and was now resolved. Dr. David W. Schall reported on the June meeting of the House of Delegates: 1) unified membership; 2) reinstated members responsible for all delinquent dues; 3) budget surplus due to M.M.A. building fund; 4) CME requirements consistent with AMA Recognition Award to be fully operative by 1980.

Dr. Richard C. Leck reported that a search committee has been directed to find lay full-time candidates for Assistant to Dr. Hanley. Dr. York was appointed to replace Dr. John F. Dougherty on the Board of Censors.

FRANK O. AVANTAGGIO, JR., M.D., *Secretary pro tem*

The regular monthly meeting of the Lincoln-Sagadahoc County Medical Society was held at The Ledges in Wiscasset, Maine on October 19, 1976. Twenty-four members and five guests were present.

The meeting was called to order by the President, Dr. David S. Hill; the minutes of the last meeting were read and accepted as read.

Communications from the M.M.A. regarding special memberships and dues were discussed. Dr. Leck moved and Dr. Evans seconded that 1977 dues be set at \$40.00; the motion was carried without dissent.

Dr. Bostwick mentioned two items discussed at the recent meeting of the Council of the New England State Medical Societies: Federal Trade Commission suits against New Haven County and Connecticut State Medical Societies for "anti-trust" activity in the ethics of professional advertising and against the American Society of Anesthesiologists for "anti-trust" activity in promulgating a Relative Value Guide.

There being no other business, Dr. Robert H. Dixon introduced Dr. C. Philip Lape, whose talk on "Diverticulitis" engendered much discussion.

GEORGE W. BOSTWICK, M.D., *Secretary*

Franklin

A meeting of the Franklin County Medical Society was held on October 4, 1976.

1. Explanation of Maine Medical Association Medical-Legal Cooperation Code Book presented to the membership.

2. Reminder of the institution of continuing medical education requirements beginning January 1, 1977, will be a requirement for membership in Maine Medical Association.

3. Discussion of possible format of meeting with Dr. David Phillips, our representative on Executive Committee, tabled for Dr. Brinkman to discuss with other members of the Society and a decision to be announced at the next County Medical Society meeting in November.

4. Dr. Page Sharp was elected to membership in the Franklin County Medical Society. His application form has been received and forwarded to the Maine Medical Association.

DANIEL K. ONION, M.D., *Secretary*

Cumberland

The 406th meeting of the Cumberland County Medical Society was held at Valle's Steak House on October 21, 1976 with Dr. Robert E. McAfee, President, presiding. Minutes of the previous meeting were omitted.

A Treasurer's Report was given. The following members were accepted for membership in the CCMS: Drs. Michael Barton,

(General Surgery), Brunswick (in transfer), Bruce A. MacDougal, (Plastic Surgeon), Portland and Carl D. Metzger, (Child Psychiatry), Portland.

Unfinished Business:

1. Professional Directory — a questionnaire was circulated to the membership as a first step in developing a professional directory of Cumberland County physicians.

2. West End Primary Medical Care Center — Dr. Harry A. Bliss reviewed the plans for opening the West End PMCC after which it was voted to apportion \$2,000.00 to the PMCC as a donation from the CCMS towards its opening costs.

3. Annual Harvest Supper — It was voted to allot an additional \$140.00 to cover the expense of the band at the annual Harvest Supper.

New Business:

1. Bylaw Change — Dr. McAfee announced at the next meeting a vote would be taken on the proposed change in the CCMS Bylaws, Chapter 1, Section 1, paragraph D — relative to Affiliate Members. The vote will be taken at the November meeting.

2. Annual High School Scholarship Fund — It was proposed, by Dr. McAfee, that CCMS consider making an annual award of \$100.00 as a scholarship award to a deserving graduating high school senior from each high school in Cumberland County. The total annual cost would therefore be \$1,300.00. The positive effect this award would have on creating interest in health care careers and the good public relations effect the award would have were emphasized by several speakers. The matter will come up for a vote at the November meeting.

3. Fluoridation Program — After a brief discussion on the fluoridation issue, it was voted that CCMS reaffirm its previous endorsement of the advisability of fluoridation of public water supplies in the Portland area.

Announcements:

1. Dr. McAfee announced that a meeting will be held on November 15, 1976 at the Portland Law School at which the Malpractice Commission will hold a hearing on a rough draft of its proposals. All are encouraged to attend.

The meeting was adjourned at approximately 9:20 p.m.

WESLEY J. ENGLISH, M.D., *Secretary*

Waldo

The regular quarterly meeting of the Waldo County Medical Society was held at Jed's Restaurant in Belfast, Maine.

Members present were Drs. Hanbury, Gay, Knuuti, Torrey and Smith.

Guest speakers were Mr. John Randazzi, Esq. and Mr. John Arnold of Central Maine Power Co. and Mr. Emil "Pat" Garrett of Safe Power for Maine organization.

Minutes of the previous meeting were read and approved.

Treasurer's report:

Balance May 1976	\$566.38
Receipts —	
Dues	6.00
Interest	16.95
Expenses — May dinner	92.73
Balance Sept.	\$496.60

There was no new or old business.

Our guests addressed themselves to the current status of nuclear power emphasizing safety, health and economic aspects.

Mr. Arnold presented a formal discussion of the operation of a nuclear power plant and the safety precautions employed.

Mr. Garrett discussed some of the hazards to health and nuclear power plants even when the safety precautions are used and also discussed the economic problems now besetting power plants utilizing nuclear fuel. He also asserted that uranium sources were largely foreign sources and these sources are no more reliable than foreign oil.

A lively discussion followed, after which the meeting adjourned.

JOSEPH A. SMITH, M.D., *Secretary*

MAINE MEDICAL ASSOCIATION

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County and Alphabetical Listing

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MDS

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MEDICAL SPECIALTIES

The following Specialties, including Family Practice, are recognized by the American Medical Association:

A	Allergy (sub-specialty of Internal Medicine)	OPH	Ophthalmology
ANES	Anesthesiology	ORS	Orthopedic Surgery
AM	Aerospace Medicine (special field of Preventive Medicine)	OTO	Otolaryngology
CD	Cardiovascular Disease (sub-specialty of Internal Medicine)	PATH	Pathology
CHP	Child Psychiatry (sub-specialty of Psychiatry)	PD	Pediatrics
CRS	Colon and Rectal Surgery	PDA	Pediatric Allergy (sub-specialty of Pediatrics)
D	Dermatology	PDC	Pediatric Cardiology (sub-specialty of Pediatrics)
DR	Diagnostic Roentgenology (special field of Radiology)	PMR	Physical Medicine and Rehabilitation
FOP	Forensic Pathology (special field of Pathology)	PS	Plastic Surgery
FP	Family Practice	P	Psychiatry
GE	Gastroenterology (sub-specialty of Internal Medicine)	PH	Public Health (special field of Preventive Medicine)
GPM	General Preventive Medicine (special field of Preventive Medicine)	PUD	Pulmonary Diseases (sub-specialty of Internal Medicine)
GS	General Surgery	R	Radiology
IM	Internal Medicine	TR	Therapeutic Radiology (special field of Radiology)
NS	Neurological Surgery	TS	Thoracic Surgery
N	Neurology	U	Urology
OBG	Obstetrics and Gynecology	00	Unspecified (retired, not in practice, no specialty reported)
OM	Occupational Medicine (special field of Preventive Medicine)	99	Other

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(Corrected To January 20, 1976)

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Read, Frank W., 9 Deering St., Portland 04101 (3)
Ready, John C., 38 Broad Cove Rd., Cape Elizabeth 04107 (3)
Record, N. Burgess, Jr., Main St., Farmington 04938 (4)
Reed, David G., 7 Washington St., Camden 04843 (7)
Reed, Howard L., 235 Madison Ave., Skowhegan 04976 (12)
Reed, James W., 18 Main St., Farmington 04938 (4)
Reel, John J., 59 So. Front St., Richmond 04357 (6)
Reeves, Edward L., 179 Sabattus St., Lewiston 04240 (1)
Reeves, Helene M., 100 Lockslev Rd., Auburn 04210 (1)
Reinstein, Paul R., Skowhegan Prof. Bldg., Skowhegan 04976 (12)
Reynolds, Arthur P., 29 Second St., Presque Isle 04769 (2)
Reynolds, John F., 325 Kennedy Dr., Waterville 04901 (6)
Rice, John D., Jr., 144 State St., Portland 04101 (3)
Richards, A. Dewey, 180 Main St., Orono 04473 (10)
Richards, Carl E., 27 June St., Sanford 04073 (15)
Richards, Henry H., 32 Valley Rd., Cape Elizabeth 04107 (3)
Richards, Lee W., Jr., 89 Hospital St., Augusta 04330 (6)
Rideout, Samuel, Green St., Fort Fairfield 04742 (2)
Robert, Roger J. P., P.O. Box 664, Biddeford 04005 (15)
Roberts, Lloyd, Penobscot Bay Medical Ctr., Rockland 04841 (7)
Robertson, Donald M., Box 188, Milbridge 04658 (14)
Robertson, George J., 1370 Turnpike St., North Andover, Mass. 01845 (6)
Robinson, Hugh P., 229 Vaughan St., Portland 04102 (3)
Rock, Daniel A., 477 Main St., Lewiston 04240 (1)
Rodriguez, Araminta M., Milo 04463 (11)
Rodriguez, Jose M., 325 Kennedy Dr., Waterville 04901 (6)
Rogers, Albert M., Georgia Warm Springs Hosp.,
Warm Springs, Ga. 31830 (3)
Rohm, Walter, Augusta State Hosp., Augusta 04330 (6)
Root, John A., 22 White St., Rockland 04841 (7)
Rosenberg, Robert P., 129 Randolph St., Bangor 04401 (10)
Rosenberg, Stanley A., 73 Deering St., Portland 04101 (3)
Rosenblatt, Stanley D., 10 High St., Lewiston 04240 (1)
Ross, Maurice, 372 Main St., Saco 04072 (15)
Roussin, William T., 48 Bacon St., Biddeford 04005 (15)
Rowan, Gilbert R., 4 Park St., Bath 04530 (8)
Rowe, Linwood M., Rumford Com. Hosp., Rumford 04276 (9)
Roy, Robert L., 325A Kennedy Mem. Dr., Waterville 04901 (6)
Royal, Albert P., Jr., 82 Maine Ave., Rumford 04276 (9)
Rubins, Nina B., E. A. Center Mem. Clinic, Steep Falls 04085 (3)
Rubins, Talivaldis, E. A. Center Mem. Clinic, Steep Falls 04085 (3)
Russell, Robert F., Castine 04421 (5)
Russell, Theodore M., Doctors Park, 89 Hospital St., Augusta 04330 (6)
Ryan, Rodney P., Second Ave., Woodland 04694 (14)
Rynne, Michael V., 2909 W. Roscoe St., Chicago, Ill. 60618 (9)

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Salvo, Anthony F., 25 Woodfield Rd., Portland 04102 (3)
Samuels, Thomas W., Maine Medical Center, Portland 04102 (3)
Sandvoss, Herman G., Union St., Kennebunkport 04046 (15)
Sanford, Theodore H., (P.A.), 97 Campus Ave., Lewiston 04240 (1)
Sangalang, Manuel G., 20 Novella St., Lewiston 04240 (1)
Santoro, Domenico A., 43 Deering St., Portland 04101 (3)
Sanzenbacher, Karl E., 325C Kennedy Mem. Dr., Waterville 04901 (6)
Saunders, Norman W., 233 Vaughan St., Portland 04102 (3)
Saunders, Sallie H., Star Route, Lincolnville 04849 (7)
Savodove, Robert F., 22 Bramhall St., Portland 04102 (3)
Sawyer, Howard P., Jr., 22 Bramhall St., Portland 04102 (3)
Sbaschnig, Robert J., Central Maine Gen. Hosp., Lewiston 04240 (1)
Scarlata, Robert W., 17 Winter St., Norway 04268 (9)
Schall, David W., 56 Baribeau Dr., Brunswick 04011 (8)
Schmidt, Lorrimer M., 13 Elm St., Augusta 04330 (6)
Schnittke, Sidney M., Porter Ave., W., Rumford 04276 (9)
Schroder, John C., 205 French St., Bangor 04401 (10)
Schumacher, William E., 14 Westwood Rd., MD "B", Augusta 04330 (6)
Schuyler, Walter B. J., 22 School St., Waterville 04901 (6)
Scolten, Adrian H., Carolina Village, Hendersontonville, N.C. 28739 (3)
Scott, Arthur M., Jr., 37 Amherst St., Biddeford 04005 (15)
Sears, Harold G., Second Ave., Woodland 04694 (14)
Sebring, Heatly D., P.O. Box 486, Waterville 04901 (6)
Seligman, Morris J., Veterans Adm., Togus 04330 (6)
Selvage, Irving L., Jr., 22 Bramhall St., Portland 04102 (3)
Senenky, Joseph P., RFD #2, Oak Ridge Dr., Augusta 04330 (6)
Sensenig, David M., 431 State St., Bangor 04401 (10)
Serrage, Elizabeth G., 87A Ocean St., South Portland 04106 (3)
Serrage, John C., Maine Medical Ctr., Portland 04102 (3)
Sewall, Elmer M., 14 Park St., Orono 04473 (10)
Sewall, Kenneth W., 2 School St., Waterville 04901 (6)
Shapiro, Benjamin L., 431 State St., Bangor 04401 (10)
Shapiro, Morrill, 7 Bramhall St., Portland 04102 (3)
Shaw, G. Patrick, 275 Main St., Biddeford 04005 (15)
Shaw, George B., 27 Broadway, Machias 04654 (14)
Shaw, John H., 131 Sewall St., Augusta 04330 (6)
Sheehan, Terrance J., Doctors Park, 89 Hospital St., Augusta 04330 (6)
Sheldon, Frank W., Wiscasset Health Ctr., Wiscasset 04578 (8)
Shelton, M. Tieche, 21 Western Ave., Augusta 04330 (6)
Shelton, Robert L., 21 Western Ave., Augusta 04330 (6)
Shems, Albert, 313 Main St., Lewiston 04240 (1)
Sherman, Fuller G., Spruce Pt., Boothbay Harbor 04538 (8)
Shields, Daniel R., 10 High St., Lewiston 04240 (1)
Shields, Thomas F., 416 Sabattus St., Lewiston 04240 (1)
Shipman, C. Frazer, Eastern Maine Med. Ctr., Bangor 04401 (10)
Shrier, Peter R., 87 Limerock St., Rockland 04841 (7)
Shubert, Alice J., 125 Leighton St., Bangor 04401 (10)
Shubert, William M., 336 Mt. Hope Ave., Bangor 04401 (10)
Shuman, Michael L., 131 Chadwick St., Portland 04102 (3)
Shurman, Hans, 10 Spring St., Dexter 04930 (10)
Siddiqui, Saleem A., 154 High St., Caribou 04736 (2)
Sidwell-Thompson, Doris M.,
R.F.D. Whittier Rd., W. Ossipee, N. H. 03890 (3)
Sieling, Walter H., Jr., 4 San Soucie Dr., Stuart, Fla. 33494 (8)
Sigafos, J. Harvey, Pleasant Point 04563 (7)
Silver, Randall H., Maine Coast Mem. Hosp., Ellsworth 04605 (5)
Simon, Pedro T., 154 High St., Caribou 04736 (2)
Simpson, Margaret R., 2 Sea Barn Rd., Cape Elizabeth 04107 (6)
Skillin, Charles E., 111 Westcott Rd., South Portland 04106 (3)
Sleeper, Francis H., 3 Colony Rd., Augusta 04330 (6)
Small, Foster C., 169 High St., Belfast 04915 (13)
Smith, A. Marshall, 489 State St., Bangor 04401 (10)
Smith, Carroll H., Delucchi Dr., Apt. 417, Reno, Nev. 89502 (2)
Smith, Christopher S., Box 232, Farmington 04938 (4)
Smith, Edgar J., 1 Park St., Fairfield 04937 (12)
Smith, Gerald R., Box 237, Naples 04055 (15)
Smith, Hugh A., Eastern Maine Med. Ctr., Bangor 04401 (10)
Smith, Jacob, 709 High St., Bath 04530 (8)
Smith, James O., 118 Front St., Bath 04530 (8)
Smith, Joseph A., High St., Camden 04843 (13)
Smith, Kenneth E., Veterans Adm., Togus 04330 (6)
Smith, Marshall E., Pratt Rd., Caribou 04736 (2)
Smith, Oney P., Post Rd., Wells 04090 (15)
Sodhi, Harbans S., Stephens Mem. Hosp., Norway 04268 (9)

Sokol, Stephen A., 10 High St., Lewiston 04240 (1)
 Solomon, Michael B., 336 Mt. Hope Ave., Bangor 04401 (10)
 Somerville, Gordon W., 165 Academy St., Presque Isle 04769 (2)
 Somerville, Robert B., 45 Hillside St., Presque Isle 04769 (2)
 Sommer, Robert G., 7 Bramhall St., Portland 04102 (3)
 Soreff, Stephen M., Maine Medical Ctr., Portland 04102 (3)
 Southall, Rogers C., 157 Pine St., Portland 04102 (3)
 Spear, William, R.F.D. No. 2, Sabattus 04280 (1)
 Starks, Pauline G., Pemaquid Point 04561 (8)
 Steele, Charles W., 472 Main St., Lewiston 04240 (1)
 Steeves, John H., Rt. 3, Skowhegan 04976 (12)
 Stein, Ernest W., 72 Main St., Pittsfield 04967 (12)
 Steinhacker, Robert, Redington-Fairview Gen. Hosp., Skowhegan 04976 (12)
 Stephenson, Richard B., 169 State St., Portland 04101 (3)
 Stevens, Harold W., c/o Fred Gross, 52 Front St., Norfolk, Mass. 02056 (15)
 Stevens, Theodore M., 148 State St., Portland 04101 (3)
 Stewart, Nancy H., Hancock St., Bar Harbor 04609 (5)
 Stewart, Winston G., Hancock St., Bar Harbor 04609 (5)
 Stimson, Barbara B., Star Route 22-282, Owl's Head 04854 (7)
 Stinchfield, Allan J., 16 E. Chestnut St., Augusta 04330 (6)
 Stitham, Linus J., 50 Main St., Dover-Foxcroft 04426 (11)
 Stocks, Joseph F., 22 Bramhall St., Portland 04102 (3)
 Stone, Charles H., III, Box 498, Greenville 04441 (11)
 Stong, Frederick V., Parkview Professional Bldg., Brunswick 04011 (8)
 Storer, Daniel P., 11 Abenaki Rd., Augusta 04330 (6)
 Stover, John H., 205 Whipple Rd., Kittery 03904 (15)
 Strach, Toffield B. J., Station A, P.O. Box 4133, Portland 04101 (3)
 Stram, Robert A., 6 E. Chestnut St., Augusta 04330 (6)
 Strauss, William T., P.O. Box 448, Hampton, N.H. 03842 (3)
 Striar, Ronald R., 94 Essex St., Bangor 04401 (10)
 Strickland, Marian L., Easy St., Canaan 04924 (12)
 Stroud, Geoffrey A., 65 Baribeau Dr., Brunswick 04011 (8)
 Strout, Warren G., 1 Fern St., Bangor 04401 (10)
 Stucki, Paul, East Vassalboro 04962 (6)
 Stuart, James H., 12 Hospital St., York 03909 (15)
 Sturtevant, Vaughn R., 325 Kennedy Dr., Waterville 04901 (6)
 Sube, Janis, 108 Elm St., Camden 04843 (7)
 Sullivan, George E., 100 College Ave., Waterville 04901 (12)
 Sundaram, Venkat R., 87A Fish St., Turner 04282 (1)
 Suyama, Eji, 58 W. Main St., Ellsworth 04605 (5)
 Swanson, Ronald A., Regional Mem. Hosp., Brunswick 04011 (8)
 Swarr, James H., 281 Main St., Biddeford 04005 (15)
 Sweatt, Linwood A., 48 Drummond St., Auburn 04210 (1)
 Swengel, Richard M., 477 Main St., Lewiston 04240 (1)
 Swett, Alfred E., Hearthside, RFD 2, No. Windham 04062 (3)
 Swett, Carlton E., P.O. Box 507, Skowhegan 04976 (12)
 Swett, Clyde I., 18 Sherman St., Island Falls 04747 (2)
 Sy, Vincente L., 125 Madison Ave., Skowhegan 04976 (12)
 Sylvester, Robert A., 103 State St., Portland 04101 (3)
 Sylvester, Stanley B., Box 548, Portland 04112 (3)
 Szelenyi, Ernest, Box C, Pownal 04069 (3)
 Szucs, Murrill M., Jr., 325 Kennedy Mem. Dr., Waterville 04901 (6)
 Tabachnick, Henry M., 110 Park Ave., Portland 04101 (3)
 Tai, Tse-Wu, RFD No. 1, South Rumford 04276 (9)
 Takach, Robert J., 325A Kennedy Dr., Waterville 04901 (6)
 Tao, Zui S., Main St., Fort Kent 04743 (2)
 Tardif, Lionel R., 9 Campus Ave., Lewiston 04240 (1)
 Taxiarchis, Louis N., R.F.D. No. 1, West Buxton 04093 (3)
 Taylor, H. Lewis, 33 Church St., Dexter 04930 (10)
 Taylor, James M., 22 Bramhall St., Portland 04102 (3)
 Taylor, Paul E., 9 Wentworth St., Kittery 03904 (15)
 Taylor, Richard C., Redington-Fairview Gen. Hosp., Skowhegan 04976 (12)
 Taylor, Richard W., St. Mary's Gen. Hosp., Lewiston 04240 (1)
 Taylor, William F., 134 U.S. Route 1, Falmouth 04105 (3)
 Tchao, Jou S., 181 Russell St., Lewiston 04240 (1)
 Telfeian, Alphonse, 92 West St., Portland 04102 (3)
 Temple, George L., Fahey St., Belfast 04915 (13)
 Tetreau, William J., 111 Westcott Rd., South Portland 04106 (3)
 Thacher, Henry C., 33 Ganneston Dr., Augusta 04330 (6)
 Thegen, W. Edward, Elm St., Bucksport 04416 (5)
 Thomas, Philip B., 1 Fern St., Bangor 04401 (10)
 Thompson, Edward C., 7 Green St., Presque Isle 04742 (2)
 Thompson, Philip P., Jr., 131 Chadwick St., Portland 04102 (3)
 Thurber, Charles F., Oak Hill Plaza, P.O. Box 802, Scarborough 04074 (3)
 Tibbetts, Otis B., 181 Gamage Ave., Auburn 04210 (1)
 Tibbetts, Otis P., Central Maine Gen. Hosp., Lewiston 04240 (1)
 Timms, G. Douglas, 1 Fern St., Bangor 04401 (10)
 Timothy, Robert P., 229 Vaughan St., Portland 04102 (3)
 Tiongson, Antonio C., 29 Malo St., Lewiston 04240 (1)
 Tiongson, Cornelia M., 185 Webster St., Lewiston 04240 (1)
 Tobin, H. Wayne, Thayer Hospital, Waterville 04901 (6)
 Torres, Rudolfo B., Redington-Fairview Hosp., Skowhegan 04976 (12)
 Torrey, Raymond L., R.F.D. No. 1, Belfast 04915 (13)
 Tounge, Harry G., Jr., 12 Union St., Camden 04843 (7)
 Tousignant, Camille, 111 Pine St., Lewiston 04240 (1)
 Toussaint, G. Peter, 143 E. Main St., Fort Kent 04743 (2)
 Towne, Charles E., 18 Common St., Waterville 04901 (6)
 Towne, John W., 325C Kennedy Mem. Dr., Waterville 04901 (6)
 Tracy, Mary J., Nido de Aguila, Puestadel Sol, Rte. 4, Santa Fe, N.M. 87501 (8)
 Trask, Henry M., 24 Hersey St., Portland 04103 (3)
 Trembly, Bruce, 325 Kennedy Dr., Waterville 04901 (6)
 Trowbridge, Mason, Jr., 77 Broadway, Bangor 04401 (10)
 True, Robert M., Maine Medical Ctr., Portland 04102 (3)
 Tsao, Wu-Ming, Veterans Adm., Togus 04330 (6)
 Turcotte, Guy N., 7 Bramhall St., Portland 04102 (3)
 Turcotte, Richard W., 95 Campus Ave., Lewiston 04240 (1)
 Turgeon, Raphael F., 367 Main St., Westbrook 04092 (3)
 Turner, Fennell P., Veterans Adm. Ctr., Togus 04330 (6)
 Turner, Harland G., Box 38, Norridgewock 04957 (12)
 Turville, Charles S., Box E, Alfred 04002 (15)
 Twadelle, Frank W., 345 Water St., Gardiner 04345 (6)
 Tyler, J. Wayne, 222 Pine St., Lewiston 04240 (1)
 Tyson, Dudley B., 91 Grove St., Bangor 04401 (10)
 Urjanis, Janis, 710 Cannons Lane, Louisville, Ky. 40206 (3)
 Vachon, Robert D., 27 June St., Sanford 04073 (15)
 Van Deventer, Wilhelm H. J., R.F.D. 3, Mere Point Rd., Brunswick 04011 (3)
 vanHoogenhuize, William H., Houlton Reg. Hosp., 45 School St., Houlton 04730 (2)
 Van Lonkhuyzen, Maurice, 131 State St., Portland 04101 (3)
 Van Pelt, John C., Eastern Maine Medical Ctr., Bangor 04401 (5)
 Veilleux, Lucien F., 325 Kennedy Dr., Waterville 04901 (6)
 Veregge, Gerald S., 89 West St., Portland 04102 (3)
 Vickers, Martyn A., 268 State St., Bangor 04401 (10)
 Vickers, Martyn A., Jr., 21 Western Ave., Augusta 04330 (6)
 Viger, Leopold A., 10 Amherst St., Biddeford 04005 (15)
 Vigue, Robert W., 183 Main St., Sanford 04073 (15)
 Viles, Wallace E., Turner 04282 (1)
 Villandry, Philip J., 22 Bramhall St., Portland 04102 (3)
 Vincze, Imre E., 336 Mt. Hope Ave., Bangor 04401 (10)
 Voss, Carlyle B., 22 Bramhall St., Portland 04102 (3)
 Vydas, Algis, Eastern Maine Medical Center, Bangor 04401 (10)
 Vydas, Joseph, Bangor Mental Health Inst., Bangor 04401 (10)
 Wadhera, Om P., Paradise Rd., Bethel 04217 (9)
 Wadhera, Usha, Paradise Rd., Bethel 04217 (9)
 Wadsworth, Richard C., 489 State St., Bangor 04401 (10)
 Wagner, Samuel L., 2 Holmes St., Winterport 04496 (10)
 Wakana, Minoru, 33 Lyndon St., Caribou 04736 (2)
 Wakefield, Robert D., St. Mary's Hosp., Lewiston 04240 (1)
 Walker, Douglass W., Maine Medical Ctr., Portland 04102 (3)
 Walsh, Andrew C., 144 State St., Portland 04101 (3)
 Ward, William W., Box 646, Rockland 04841 (7)
 Ware, Donald E., 17 Winter St., Norway 04268 (9)
 Ware, Roland G., Jr., 22 Bramhall St., Portland 04102 (3)
 Warren, Henry S., Derby Rd., Islesboro 04848 (7)
 Wasgatt, Wesley N., 41 Talbot Ave., Rockland 04841 (7)
 Watanabe, Tatsuo, 325 Kennedy Mem. Dr., Waterville 04901 (6)
 Waterman, Dorothy, Waldoboro 04572 (7)
 Waterman, Richard, Waldoboro 04572 (7)
 Watt, Thomas L., 316 State St., Bangor 04401 (10)
 Weaver, Donald J., 121 Main St., Thomaston 04861 (7)
 Weaver, Michael L., 10 Water St., Brunswick 04011 (3)
 Webber, Isaac M., 29 Deering St., Portland 04101 (3)
 Webber, John R., 6 Northport Ave., Belfast 04915 (13)
 Webber, Peter B., 233 Vaughan St., Portland 04102 (3)
 Webber, Wedgwood P., 37 Applegate Lane, Falmouth Foreside 04105 (1)
 Wheelwright, Henry J., Augusta Gen. Hosp., Augusta 04330 (6)
 White, Chester W., Jr., 22 Bramhall St., Portland 04102 (3)
 White, Henry O., 22 White St., Rockland 04841 (7)
 White, Leland M., 18 Pleasant St., Caribou 04736 (2)
 White, Richard L., 7 Bramhall St., Portland 04102 (3)
 White, William J., 1 Mitchell Rd., South Portland 04106 (3)
 Whitney, Philip G., 233 Vaughan St., Portland 04102 (3)
 Whittier, Alice A. S., 143 Neal St., Portland 04102 (3)
 Wickenden, John W., 22 White St., Rockland 04841 (7)
 Wight, Donald G., 30 Mitchell Rd., South Portland 04106 (3)
 Wilbur, Herbert T., Jr., 100 Main St., Southwest Harbor 04679 (5)
 Wilder, William D., Box 2146, Augusta 04330 (6)
 Wilkis, Joseph L., 260 Western Ave., South Portland 04106 (3)
 Williams, Edward P., 3 Mechanic St., Houlton 04730 (2)
 Williams, Thomas W., 22 White St., Rockland 04841 (7)
 Williamson, Elizabeth E., Blue Hill 04614 (5)
 Williamson, Russell G., Blue Hill Mem. Hosp., Blue Hill 04614 (5)

Wilson, Donald W., 52 Gilman St., Portland 04102 (3)
Wilson, G. Ivan, 48 Court St., Houlton 04730 (2)
Wilson, Robert D., Mt. Desert Island Hosp., Bar Harbor 04609 (5)
Wilson, Robert W., Box 962, Jefferson 04348 (6)
Wilson, William S., 263 State St., Bangor 04401 (10)
Winchenbach, Francis A., 910 Washington St., Bath 04530 (8)
Winkelbauer, Rudolf G., 62 Baribeau Dr., Brunswick 04011 (3)
Wise, Joe R., Jr., 263 State St., Bangor 04401 (10)
Witwer, Timothy S., Transalpine Rd., Lincoln 04457 (10)
Wolf, Kenneth P., 181 Russell St., Lewiston 04240 (1)
Wong, Lee Man, 6 Green St., Fort Fairfield 04742 (2)
Wood, George W., III, 263 State St., Bangor 04401 (10)
Woodcock, John A., 109 State St., Bangor 04401 (10)
Woodruff, Alan F., 16 Summer St., Rockland 04841 (7)
Worthing, Verla E., 199 Main St., Thomaston 04861 (7)
Wright, Herbert J. Jr., 45 Golder St., Lewiston 04240 (1)

Wyman, David S., 233 Vaughan St., Portland 04102 (3)
Wyman, Edwin T., Sebec 04481 (11)

Yaghmai, Madjid, Cary Mem. Hosp., Caribou 04736 (2)
Yap, Victor, 18 Garden Circle, Caribou 04736 (2)
Yates, William T., Box 525, Wilton 04294 (4)
York, Elihu, 62 Baribeau Dr., Brunswick 04011 (8)
Young, E. Stanley, Poland Spring 04274 (1)
Young, John, Paradise Rd., Bethel 04217 (9)
Young, William J., Maine Medical Ctr., Portland 04102 (3)
Youngs, David D., 260 Western Ave., South Portland 04106 (3)

Zanca, Ralph, 405 Center St., Auburn 04210 (1)
Zerner, John, 260 Western Ave., South Portland 04106 (3)
Zolov, Benjamin, 296 Congress St., Portland 04101 (3)
Zorick, Frank J., 489 State St., Bangor 04401 (10)

PAST PRESIDENTS

Maine Medical Association

*Isaac Lincoln, M.D., Brunswick	April-June, 1853	*James A. Spalding, M.D., Portland	1917-1918
*James McKeen, M.D., Topsham	1853-1854	*George H. Coombs, M.D., Waldoboro	1918-1919
*Charles Millett, M.D., Lewiston	1854-1855	*H. B. Mason, M.D., Calais	1919-1920
*Joseph H. Estabrook, M.D., Camden	1855-1856	*Theodore E. Hardy, M.D., Waterville	1920-1921
*Hosea Rich, M.D., Bangor	1856-1857	*Addison S. Thayer, M.D., Portland	1921-1922
*Gilman Daveis, M.D., Portland	1857-1858	*L. T. Snipe, M.D., Bath	1922-1923
*J. C. Bradbury, M.D., Old Town	1858-1859	*C. A. Moulton, M.D., Hartland	1923-1924
*H. H. Hill, M.D., Augusta	1859-1860	*F. W. Mann, M.D., Houlton	1924-1925
*T. G. Stockbridge, M.D., Bath	1860-1961	*J. D. Phillips, M.D., Southwest Harbor	1925-1926
*H. M. Harlow, M.D., Augusta	1861-1862	*L. P. Gerrish, M.D., Lisbon Falls	1926-1927
*Alonzo Garcelon, M.D., Lewiston	1862-1863	*Herbert F. Twitchell, M.D., Portland	1927-1928
*J. T. Gilman, M.D., Portland	1863-1864	*Frank Y. Gilbert, M.D., Portland	1928-1929
*N. P. Monroe, M.D., Belfast	1864-1865	*Delbert M. Stewart, M.D., South Paris	1929-1930
*Amos Nourse, M.D., Bath	1865-1866	*Charles B. Sylvester, M.D., Portland	1930-1931
*S. H. Tewksbury, M.D., Portland	1866-1867	*Ernest V. Call, M.D., Lewiston	1931-1932
*Cyrus Briggs, M.D., Augusta	1867-1868	*E. Delmont Merrill, M.D., Dover-Foxcroft	1932-1933
*I. T. Dana, M.D., Portland	1868-1869	*Warren E. Kershner, M.D., Bath	1933-1934
*D. McRuer, M.D., Bangor	1869-1870	*Edwin W. Gehring, M.D., Portland	1934-1935
*B. F. Buxton, M.D., Warren	1870-1871	*John L. Johnson, M.D., Bangor	1935-1936
*A. J. Fuller, M.D., Bath	1871-1872	*Frederick T. Hill, M.D., Waterville	1936-1937
*A. P. Snow, M.D., Winthrop	1872-1873	*Ralph W. Wakefield, M.D., Bar Harbor	1937-1938
*A. F. Page, M.D., Bucksport	1873-1874	*Willard H. Bunker, M.D., York Harbor	1938-1939
*Thomas H. Brown, M.D., Paris	1874-1875	*George L. Pratt, M.D., Fairfield	1939-1940
*J. H. Bates, M.D., Yarmouth	1875-1876	*Thomas A. Foster, M.D., Portland	1940-1941
*E. F. Sanger, M.D., Bangor	1876-1877	*P. L. B. Ebbett, M.D., Houlton	1941-1942
*T. H. Jewett, M.D., South Berwick	1877-1878	*Carl H. Stevens, M.D., Belfast	1942-1943
*M. C. Wedgwood, M.D., Lewiston	1878-1879	*Oscar F. Larson, M.D., Machias	1943-1944
*S. C. Gordon, M.D., Portland	1879-1880	*R. V. N. Bliss, M.D., Blue Hill	1944-1945
*William Warren Greene, M.D., Portland	1880-1881	*Adam P. Leighton, M.D., Portland	1945-1946
*A. K. P. Meserve, M.D., Buxton	1881-1882	*John O. Piper, M.D., Waterville	1946-1947
*George E. Brickett, M.D., Augusta	1882-1883	*Stephen A. Cobb, M.D., Sanford	1947-1948
*Oren A. Horr, M.D., Lewiston	1883-1884	*Forrest B. Ames, M.D., Bangor	1948-1949
*Thomas A. Foster, M.D., Portland	1884-1885	Ralph A. Goodwin, Sr., M.D., Auburn	1949-1950
*Sumner Laughton, M.D., Bangor	1885-1886	Foster C. Small, M.D., Belfast	1950-1951
*J. B. Walker, M.D., Thomaston	1886-1887	*C. Harold Jameson, M.D., Rockland	1951-1952
*Frederick C. Thayer, M.D., Waterville	1887-1888	*Eugene H. Drake, M.D., Portland	1952-1953
*Stephen H. Weeks, M.D., Portland	1888-1889	Norman H. Nickerson, M.D., Greenville	1953-1954
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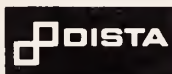
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Indications: Tension and anxiety states; somatic complaints which are concomitants of emotional factors; psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation; symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathol-

ogy; spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome; convulsive disorders (not for sole therapy).

Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency

and/or severity of grand mal seizures may require increased dosage of standard anti-convulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Keep addiction-prone individuals under careful

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Indications: Relief of anxiety and tension occurring alone or accompanying various disease states.

Contraindications: Patients with known hypersensitivity to the drug.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. As with all CNS-acting drugs, caution patients against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving). Though physical and psychological dependence have rarely been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions), following discontinuation of the drug and similar to those seen with barbiturates, have been reported.

Usage in Pregnancy: Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.

Precautions: In the elderly and debilitated, and in children over six, limit to smallest effective dosage (initially 10 mg or less per day) to preclude ataxia or oversedation, increasing gradually as needed and tolerated. Not recommended in children under six. Though generally not recommended, if combination therapy with other psycho-

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tropics seems indicated, carefully consider individual pharmacologic effects, particularly in use of potentiating drugs such as MAO inhibitors and phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions (e.g., excitement, stimulation and acute rage) have been reported in psychiatric patients and hyperactive aggressive children. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relation-

ship has not been established clinically.

Adverse Reactions: Drowsiness, ataxia and confusion may occur, especially in the elderly and debilitated. These are reversible in most instances by proper dosage adjustment, but are also occasionally observed at the lower dosage ranges. In a few instances syncope has been reported. Also encountered are isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent and generally controlled with dosage reduction; changes in EEG patterns (low-voltage fast activity) may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice and hepatic dysfunction have been reported occasionally, making periodic blood counts and liver function tests advisable during protracted therapy.

Usual Daily Dosage: Individualize for maximum beneficial effects. *Oral—Adults:* Mild and moderate anxiety and tension, 5 or 10 mg *t.i.d.* or *q.i.d.*; severe states, 20 or 25 mg *t.i.d.* or *q.i.d.* *Geriatric patients:* 5 mg *b.i.d.* to *q.i.d.* (See Precautions.)

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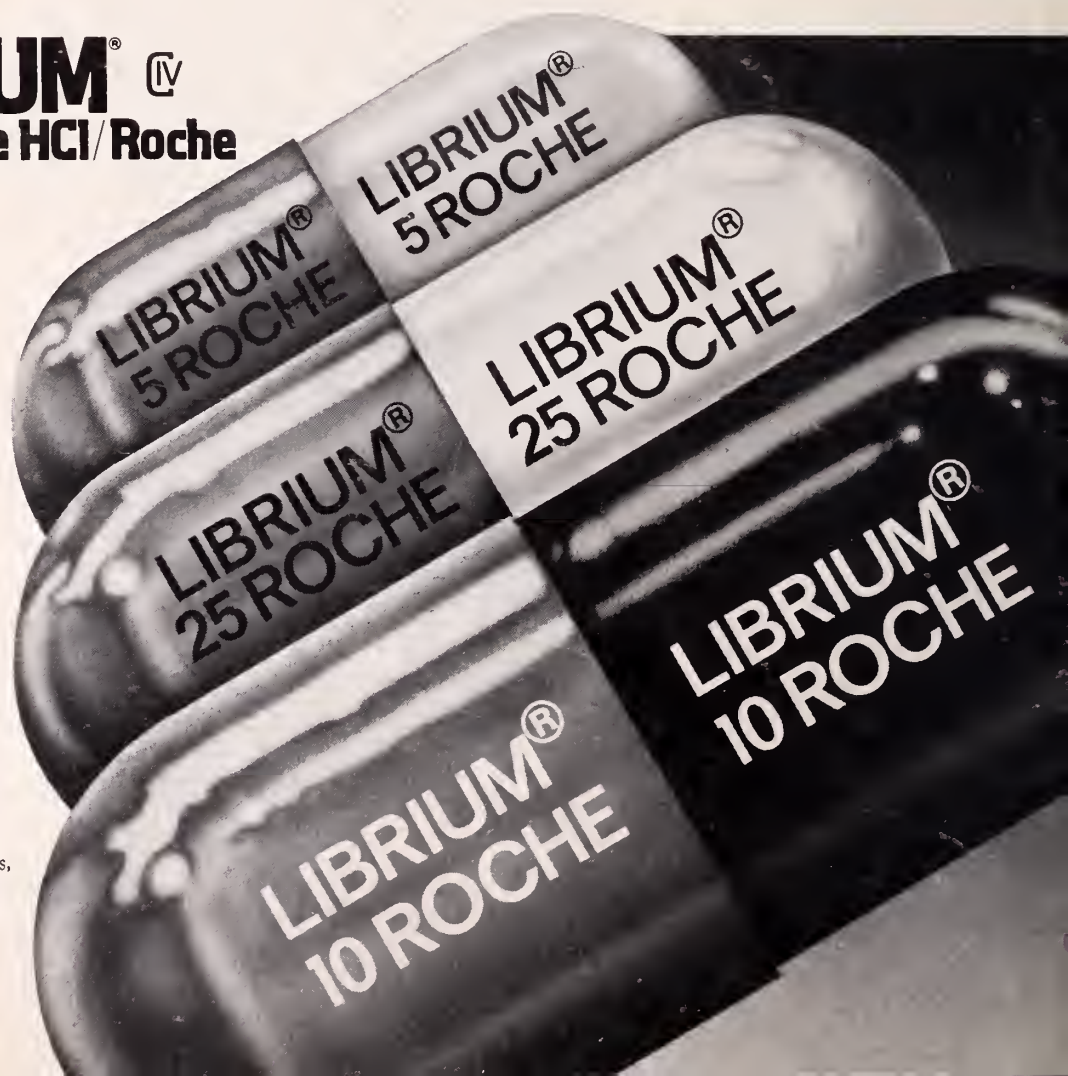
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